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THE CHICAGO MEDICAL SCHOOL
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# ENDOCRINE ASPECTS OF HEPATIC DISEASE*

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The relationship of the liver to endocrine function can be considered from several aspects. These include impairment of hormone inactivation resulting in signs and symptoms ascribable to hormone excess, clinical syndromes simulating endocrine disease in patients with hepatic cirrhosis, and the effects of hormones on the liver.

### Hormone Excess Resulting from Impairment of Hepatic Inactivation

Evidence of an effect by the liver on endocrine glands and their products has come from both clinical[1] and experimental sources[2]. The most dramatic and compelling evidence has been related to the effects of the liver on estrogen metabolism[1–20]. Males with cirrhosis of the liver show a high incidence of gynecomastia, testicular atrophy, loss of libido and changes in the prostate[1,3,6,7,13–16]. Cirrhotic females may have menstrual irregularities, breast and endometrial changes[1]. All of these changes have been considered to be related to impaired estrogen inactivation by the liver[1]. Spider nevi and palmar erythema also have been attributed to a hyperestrogenic state[9–12]. Barr and Sommers[17], in a recent autopsy study of 100 patients with cirrhosis, concluded that 85% of the female patients and 90% of the males showed histologic "evidence of estrogenic effects." Studies of hormone excretion in cirrhotics have revealed, in some instances, increased urinary estrogen[1–12], decreased urinary androgen[3,4] and 17-ketosteroid[1,2–8,21] levels. A variable tendency to decreased urinary gonadotropin levels has been described[1,6,7].

Abnormal distribution and amount of body hair has been emphasized in descriptions of cirrhosis[13,14,18–20]. Particular reference[13] has been made to the lack of chest hair frequently observed in cirrhotic males with the implication that this well known phenomenon results from cirrhosis. Chvostek[18], Eppinger[19] and Spellberg[20] have stated that pectoral alopecia in "alcoholic" cirrhosis is not a result of the cirrhosis but appears to be a constitutional feature antedating the cirrhosis. We likewise have not seen loss of chest hair as a result of the disease. When there is pectoral alopecia in a cirrhotic patient, it has been our consistent experience that it has been a lifelong feature[22].

Bean[9–12] has summarized the evidence for the relationship of spider nevi to increased blood estrogen levels. Other evidences for hyperestrogenism in cirrhosis, the occurrence of these vascular lesions in pregnancy[11], and the intensification of the "spider nevi" in cirrhotics who receive estrogenic hormone[9] all support the relationship of hyperestrogenism to the occurrence of spider nevi. Such lesions are observed in approximately 70%

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of patients with cirrhosis[10]. Less frequently they are seen in patients with hepatitis[10]. They have been reported in a patient with extensive metastatic carcinoma of the liver[23]. Prominent spider nevi are very rare in normals. These lesions are seen characteristically on the upper extremities, face, neck and upper trunk[10]. The basis for this distribution is as yet unknown, although Eppinger[19] has emphasized that this distribution conforms to the region drained by the superior vena cava.

Palmar erythema appears to be somewhat less specific. Although common in patients with cirrhosis, and with severe hepatitis, as well as in pregnancy, it is also noted in patients with rheumatoid arthritis and, not infrequently, in normals[13]. It is our impression that palmar erythema which includes the finger tips and particularly the dorsum of the finger tips is somewhat more suggestive of liver disease than the reddening of only the thenar and hypothenar eminences.

Gynecomastia occurs in 10%[12] to 40%[13] of male patients with cirrhosis of the liver. It has also been observed in association with viral hepatitis[24], metastatic carcinoma, starvation and the hepatic dysfunction of congestive failure[25,26]. Cirrhotic patients with gynecomastia have also shown increased urinary estrogens[1–8] with a distinct increase in the excretion of "free" or unconjugated hormone[3]. No direct correlation, however, has been found by Rupp and his associates[7] between the urine estrogen level in cirrhotic patients and the presence of gynecomastia.

Testicular atrophy is a common feature of cirrhosis[1,6,7,13,26–28]. Clinical evidence is found in 40% or more[27] of cirrhotic patients. Seventy per cent[27] of cirrhotics show histologic abnormalities including atrophy of the germinal epithelium, inhibition of spermatogenesis and interstitial fibrosis. Although this phenomenon also has been attributed to hyperestrogenism[17], Pincus and his associates[6] have cast doubt on this mechanism. These workers have suggested that depressed pituitary gonadotropic function, not necessarily the result of hyperestrogenism, accounts for the testicular atrophy. They also suggest that androgen deficiency may be at least as important as estrogen excess or gonadotropin deficiency.

Changes in the prostate or cirrhotic patients have been studied by several workers[17,27–30]. Wu[29] has reported an increased incidence of "nodular" hyperplasia of the prostate. Stumpf and Wilens[30] and Barr and Sommers[17], on the other hand, have emphasized an inhibitory effect of cirrhosis on prostate enlargement. These latter authors noted, in a study of a large number of autopsies, that the incidence and degree of the prostatic hypertrophy in cirrhotics was significantly lower than in a non-cirrhotic control group. Stumpf and Wilens[30] suggested that "protractedly elevated estrogen levels or other hormonal imbalance may be responsible for the lower incidence of prostate hypertrophy" in cirrhotic patients. Barr and Sommers[17] have drawn similar conclusions. They also have emphasized the high incidence of "sclerotic atrophy" of the testis, a change ascribed by Franks[31] to estrogen effect.

The clinical evidences of hyperestrogenism in cirrhotic patients have been related to the role normally played by the liver in estrogen metabolism[1,2]. Experimentally, it has been demonstrated that estrogenic hormones are inactivated by the normal liver[2]. When ovarian hormones are released into the portal circulation by transplanting ovaries into the mesentery[32] or spleen[33] of gonadectomized female rats, estrus does not occur. Ovarian transplants to the axilla[32], however, permit the occurrence of estrus. Likewise, ovarian transplants to the spleen of the male rat do not result in testicular atrophy, while subcutaneous ovarian transplants do produce atrophy of the testis[34]. Gonadectomized female rats with experimental liver damage from hepatotoxins[35], malnutrition[5,36] or partial hepatectomy[37] require less estradiol administration for uterine weight increase and vaginal cornification than do animals with normal livers. Biskind and Biskind[5] and Segaloff and Segaloff[38] found that malnutrition, even without overt liver damage, may result in simi-

larly decreased ability of the liver to inactivate estrogenic hormones. Rats fed diets deficient in the vitamin B group show impaired ability to inactivate estrogen released from intrasplenic pellet implants[5]. Administration of Brewer's yeast, riboflavin or niacin to such animals restored the ability of the liver to inactivate the hormone[5,38]. Drill and Pfeiffer[39] have challenged the specificity of these vitamin deficiencies and emphasized the importance of inanition in impairing the hepatic ability to inactivate estrogens.

Studies with hepatic vein catheterization in humans receiving large doses of estrogens[40] and the increased urine excretion of estrogens[1-8] in cirrhotics likewise support the importance of the liver in inactivating estrogens.

*In vitro* experiments[41-45] have also demonstrated the ability of the liver to inactivate estrogenic hormones. Zondek[4] has shown that estrogens are rendered inert by incubation with rat liver pulp. This ability is also found in a cell-free extract of liver, but is destroyed by heating.[42]. This enzyme-like property of liver tissue was called "estrinase" by Zondek[41,42]. Liver slices have also been shown to possess this property[43]. Twombly and Taylor[44] and Tagnon and his associates[45] have shown that human liver tissue obtained at laparotomy also possessed estrogen-inactivating capacity. Studies with animal livers have shown that estrone and estradiol are most effectively inactivated, while estriol is less completely inactivated[2].

The changes effected in estrogenic hormones by hepatic enzymes include conjugation of the hormone with glucuronate ("reversible" inactivation) and changes in the steroid molecule proper ("irreversible" inactivation)[2].

Another role played by the liver in the metabolism of estrogens is that of removal of the hormone from the blood and excretion into the bile[46-51]. Impaired excretion, as well as impaired inactivation by the liver, may contribute to the apparent hyperestrogenic state seen in cirrhotic patients.

Biskind and Biskind[5] also have demonstrated that testosterone is inactivated by the normal liver. The ability of animals to inactivate androgenic hormone appears to be retained after the ability to metabolize estrogens has been lost[5]. It also has been shown[52] that cirrhotic patients are as able to convert testosterone to 17-ketosteroids as other chronically ill patients without hepatic disease, but less well than normals. This is consistent with the formulation of Biskind and Biskind[5] that the endocrine stigmata of cirrhosis ascribable to impaired ability to inactivate estrogens may be compounded by persistent ability to inactivate androgenic hormones.

Retention of salt and water may also be related to abnormal hormone metabolism in hepatic disease[13]. Although hypoalbuminemia and portal hypertension may contribute importantly to the ascites of cirrhosis, there is increasing evidence for the role of endocrine factors in the accumulation of sodium and water by cirrhotic patients[53-56].

The impairment of salt and water excretion in hepatic disease also has been demonstrated by clinical and experimental studies. Several authors[57,58] have commented on the diuresis which is noted during the recovery phase of viral hepatitis. Adlersberg and Fox[59] found an abnormal retention of water when "water tolerance tests" were performed on patients with severe hepatic disease. Ralli and her associates[60] have demonstrated the excretion of increased amounts of an anti-diuretic factor in the urine of patients with ascites due to cirrhosis. This substance, presumed to be the anti-diuretic hormone of the hypophysis, has been considered[60] to contribute to the ascites and edema of cirrhotic patients. Impaired ability of the diseased liver to inactivate anti-diuretic hormone recently has been demonstrated[61] in studies with cirrhotic rat liver. It has also been suggested[63] that the increased levels of ferritin (VDM), found in ascitic fluid of cirrhotic patients may, through the stimulation of the production of anti-diuretic hormone, contribute to the edema and ascites of cirrhosis.

In a recent review by Welt[61], however, the concept that anti-diuretic hormone plays an important role in cirrhotic edema or ascites has been challenged. Recent studies[63,64] have shown that there is "no delay in the inactivation of and no increase in sensitivity to anti-diuretic hormone in patients with liver disease"[61]. Welt[61] has suggested that any evidence of increased anti-diuretic hormone secretion is better explained as a response to the "physiologic stimulus created in some fashion by the primary disorder," such as decrease in plasma volume.

More relevant to the occurrence of edema and ascites is the mounting evidence for the role of excess mineralocorticoid activity[53-56,65-70]. A defect in the excretion of sodium by cirrhotic patients has been observed by Eisenmenger and his associates[53,54]. This has been shown to be associated with the urinary excretion of increased amounts of a substance which was salt retaining when injected into rats, and which has been since found to be aldosterone[65-72]. Studies by several groups have revealed that cirrhotics[66-72] with ascites excrete significantly larger amounts of aldosterone than do normals. It is of particular interest that abdominal paracentesis is often followed by an increase in the rate of aldosterone excretion[68]. While the mechanism for the abnormal urinary aldosterone levels in cirrhotic patients is not clear, it is presumably related, at least in part, to the failure of the diseased liver to inactivate this hormone. Both the rat and the human liver have been shown[71] to possess the ability to inactivate aldosterone *in vitro*. Impaired ability to inactivate other steroids may also contribute to the salt and water retention of cirrhotics since glucocorticoids and estrogenic hormones also can decrease renal excretion of sodium[13]. Successful attempts to treat intractable ascites by removal of adrenocortical factors have included suppression of adrenal cortical function with amphenone[69] and bilateral adrenalectomy[70]. Such procedures, in the present state of our knowledge carry hazards which outweigh potential benefit to be derived from them.

Hydrocortisone and other adrenal cortical steroids also have been shown to be inactivated by the liver[73-80]. *In vitro*[72-75], and perfusion[75] studies have demonstrated the ability of normal liver and impaired ability of cirrhotic liver to metabolize adrenal cortical hormones. Blood[77-79] and urine[76] levels of 17-hydroxycorticoids are elevated in patients with liver disease. Infusion of hydrocortisone into cirrhotic patients results in a slower than normal rate of disappearance and in a subnormal rate and degree of inactivation[78,79]. The apparent defect in inactivation, according to Brown and his associates[78-79] is related to the inability to reduce ring A, rather than to impaired conjugation. The impaired ability to inactivate glucocorticoids is of interest in view of the observations of Bongiovanni and Eisenmenger[80] that some young females with cirrhosis have clinical features suggesting hyperadrenocorticism.

The metabolism of other hormones is also related to the liver, but with less apparent clinical significance than in the case of the foregoing. Insulin, labelled with $I^{131}$ has been shown to be concentrated in the liver *in vivo*[81] and to be inactivated by liver tissue *in vitro*[82]. Mirsky[82] has attempted to relate the "insulinase" system of the liver to insulin resistance, and, indeed, to the pathogenesis of diabetes.

Thyroid hormone metabolism is also effected by the liver. Studies with stable[83,84,85] and $I^{131}$-labelled thyroxine[86,87] in animals have revealed that this hormone is converted by the liver to another compound ("Compound U") which is excreted in the bile. Briggs, Taurog and Chaikoff[86] have suggested that this represents a simple detoxification mechanism. A similar biliary excretion of a metabolic product of thyroxine has been demonstrated in humans[88], but no evidence that this phenomenon has clinical significance has been developed. It is of interest that cirrhotics have been shown[89] to have an increased thyroidal uptake of $I^{131}$. This has been ascribed by Shipley and Chudzik[80] to "iodine starvation" rather than to thyroid dysfunction.

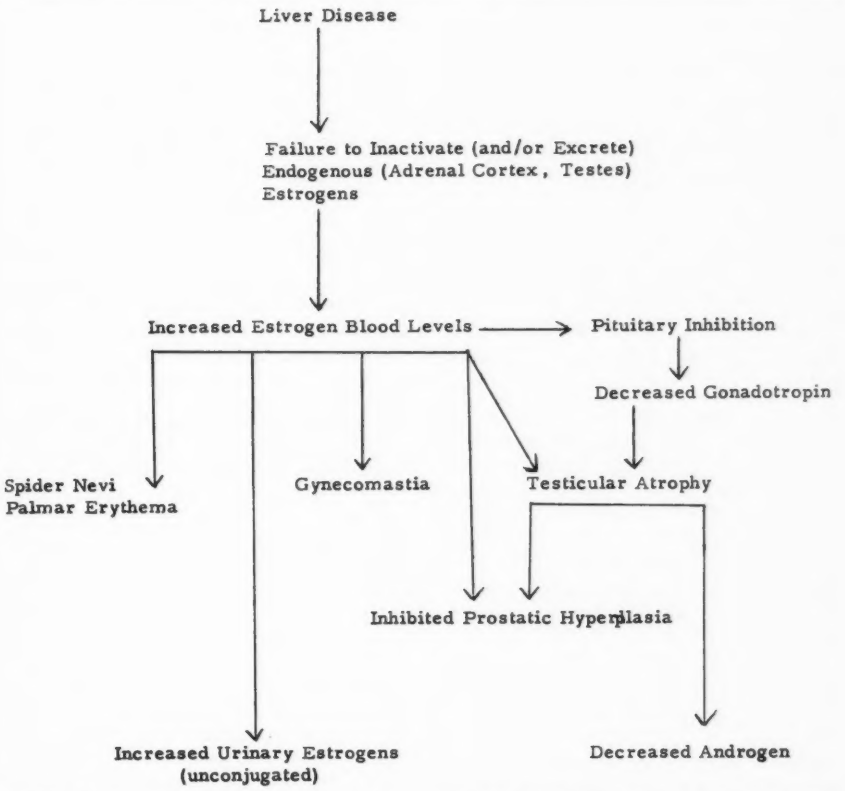


FIGURE 1. Diagrammatic Representation of Pathogenesis of Spider Nevi, Gynecomastia, Testicular Atrophy and Prostatic Changes in Cirrhotic Males. (Modified from Sherlock[13].)

### Clinical Syndromes Simulating Endocrine Disease

There are several syndromes occurring in patients with liver disease which simulate endocrine disease. Hypoglycemia has been emphasized as a possible manifestation of acute hepatic necrosis[91,92], cirrhosis[93], carcinoma of the liver[94-96] and of congestive heart failure[97]. In the experience of the author[98], however, hypoglycemia is a rare complication of hepatic disease.

The impairment of glucose tolerance in patients with hepatic disease is also well known. The curve described[93] as characteristic includes a low or normal fasting level, abnormally high levels at 1, 2 and even 3 hours, but a level lower than the fasting at the 4th or 5th hour. Fasting hyperglycemia also has been demonstrated in patients with cirrhosis of the liver[98–100]. Such patients are difficult to distinguish from true diabetics. A procedure which has been suggested as an aid to this differential diagnosis is the intravenous glucose tolerance test with[101] or without[102] the determination of serum inorganic phosphorous levels. The results of this procedure, however, are often inconclusive. Leevy and his associates[100] have emphasized the diagnostic value of the reversibility of the "diabetic" syndrome in cirrhotic patients. This "hepatic pseudodiabetes" may be the result of pancreatic destruction, due

to the pancreatitis so common in alcoholics, or may be a true diabetes coincidental with and worsened by the cirrhosis. More theoretical are the possibilities that it may represent "steroid diabetes" caused by the increased glucocorticoid levels resulting from impaired hepatic inactivation or an impairment of the role the liver has been shown[103] to play in peripheral utilization of glucose. Reference has been made above to a syndrome simulating hyperadrenocorticism in young females with post-necrotic cirrhosis.

**Effects of Hormones on the Liver**

A number of hormones have been shown to effect the liver. It is well known that injection of anterior pituitary extract produces fatty metamorphosis of the liver in experimental animals[104–106]. This adipokinetic property has been shown to reside, particularly, in the pituitary fraction containing somatotropin[106]. Stetten[107] has demonstrated that the fatty livers resulting from administration of pituitary extracts represent fat mobilized from the depots. The author has observed fatty metamorphosis in liver biopsy specimens obtained from acromegalic patients.

Hepatic functional and structural abnormalities have long been emphasized in hyperthyroidism[108–113]. Impaired galactose tolerance[108,109], BSP excretion[110], and hippuric acid synthesis[111] as well as hypoalbuminema[113] have been observed frequently in patients with this disease[113]. Fatty metamorphosis[113], foci of necrosis[113] and even cirrhosis of the liver[113,114] have been demonstrated at autopsy in thyrotoxic patients. It even has been suggested[116] that thyroid storm may be a manifestation of hepatic failure. The pathogenesis of the hepatic abnormality is obscure. Administration of thyroid hormone to experimental animals potentiates the hepatic lesions resulting from hepatotoxins[117], and anoxia[118], but does not produce demonstrable hepatic lesions when given alone. It has been suggested[115] that hyperthyroidism produces hepatic abnormality through circulatory alterations, relative anoxia[119], dietary deficiency resulting from the increased metabolic rate[119] or though aggravation of coincident disease[112,113]. It should be recalled that needle biopsy studies of the liver do not reveal the abnormalities observed at autopsy[120].

Studies of the effects of sex hormones have revealed somewhat inconsistent results. Estrogenic hormones have been found[121–124] to inhibit the development of nutritional fatty metamorphosis. Male rats are more susceptible than female rats to this variety of hepatic damage[123]. Castrated females lose their "protection," which may be restored by the administration of estradiol. Conversely, hepatic damage resulting from ethionine administration can be more readily induced in the female than in the male rat[125]. We are aware of no clinical studies clarifying the relationship between sex and liver disease. The lesser frequency of "alcoholic" cirrhosis in females may be related to lesser alcoholism or to a lesser degree of susceptibility to this cause of hepatic disease. It is of interest, that the severity of apparent hepatitis in Denmark was greater in post- than in premenopausal patients[126]. Young girls with cryptogenic post-necrotic cirrhosis, on the other hand, may be worsened by estrogen administration[127]. Thus, estrogenic hormone appears to "protect" animals from the effect of choline deficient diets to potentiate experimental hepatotoxic liver injury and to have an unclear clinical effect.

Testosterone has been used in the therapy of hepatic disease as replacement for the testicular deficiency described above and for its anabolic properties[128,129]. The evidence remains unconvincing that testosterone has a favorable effect on the hepatic disease *per se*. Methyltestosterone[230] and methylestrenolone[131] have been reported to produce jaundice, "cholangiolytic" in type.

It has long been known that fatty metamorphosis of the liver is frequent in diabetic patients[132–134]. This has been traditionally ascribed to insulin deficiency and the resultant impairment in carbohydrate metabolism[133-135]. Experimental, untreated pancreatectomy-diabetes is indeed characterized by fatty meta-

morphosis[136]. Clinical evidence has been less clear. While diabetics frequently have fatty livers, "well-controlled," as well as "poorly-controlled" diabetics may show fatty metamorphosis[137]. It was our experience[137], as well as that of Sherlock and her associates[138], that obese, insulin-insensitive diabetics were particularly likely to show fatty metamorphosis. It has been suggested[137–138] that this fatty metamorphosis may be a manifestation of anterior pituitary hormone activity.

Pancreatectomized dogs maintained on insulin do not develop the early fatty metamorphosis that untreated dogs do[136]. Even animals receiving insulin, however, develop fatty metamorphosis after 12 to 14 weeks[136]. Choline, or other "'lipotropic agents" or oral pancreatic extract prevents these delayed fatty livers[139]. This delayed fatty metamorphosis has been considered the result of choline deficiency secondary to lack of the exocrine pancreatic secretion. While clinical counterparts of this have been scarce, patients with chronic pancreatitis do have frequent fatty metamorphosis of the liver. Since such patients are often alcoholics, however, the fatty metamorphosis cannot be considered, soley, a result of the pancreatic insufficiency[134].

Adrenal cortical steroids have also been shown to effect the liver[130–144]. The "permissive"[142] role of the adrenal cortex is apparent to the essentiallity of an intact adrenal cortex or adequate replacement therapy for the adipokinetic effect of growth hormone[105,140,141]. Fatty metamorphosis has been observed[143,144] in animals receiving large doses of ACTH or cortisone. Conversely, cortisone has been shown[145] to inhibit the development of nutritional fatty metamorphosis.

## SUMMARY


1. The relationship of the liver to the endocrines should be considered in terms of (a) the effect of the liver on hormones (b) syndromes simulating endocrine disease in patients with hepatic disease and (c) the effects of hormones on the liver.

2. Gonadal and adrenal steroids, antidiuretic hormone, insulin and thyroxine have been shown to be metabolized by the liver. Failure to inactivate and/or excrete some of these hormones may occur in liver disease and produce clinical abnormalities as shown below.

(a) Estrogen excess resulting from mechanism is the apparent basis of the following:
   1. Testicular atrophy
   2. Gynecomastia
   3. Libido loss
   4. Prostatic hypertrophy inhibition
   5. Menstrual disturbance
   6. Edema (and ascites) in cirrhosis is related, at least in part, to impaired inactivation of aldosterone and perhaps of other sodium retaining estrogens. The role of anti-diuretic hormone excess in water retention is still uncertain.

3. The chief syndromes simulating endocrine disease in cirrhotic patients are (a) spontaneous hypoglycemia (b) "hepatic pseudodiabetes" and (c) apparent hyperadrenocorticism perhaps related to impaired inactivation of glucocorticoids.

4. The hormones which have a demonstrable effect on the liver include (a) somatotropin (b) corticotropin (c) estrogens (d) androgens (e) thyroid hormone (f) insulin (g) adrenal cortical steroids.


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# BLOOD GROUPS AND HUMAN GENETICS*

**RUTH SANGER, B.Sc., Ph.D.** and R. R. RACE, Ph.D., M.R.C.S., F.R.S.****

## I. Some Fundamental Aspects

The building of the science of genetics has surely been one of the great achievements of the last 100 years. The knowledge has been based on work with many organisms: — plants, flies, mice, molds, bacteria, viruses and even bacteriophage — but human genetics, because of particular difficulties, has lagged rather far behind.

I suppose one of the very first steps in studying the genetics of any species is to find out how many chromosomes there are. Until a year ago we were told, and we believed, that we had 24 pairs of chromosomes — 23 autosomal pairs and 1 sex pair; but as a result of work in Sweden and in England it seems that we must now become reconciled to the idea that we have only 23 pairs. Though we now have only 22 autosomal pairs, happily we still have the sex pair.

Several of the basic phenomena of inheritance can be illustrated in man by examples taken from the blood groups. In fact, it would be possible to give a fairly good account of the principles of genetics using only blood groups as examples.

The *ABO* groups must have been the first normal human characters to illustrate Mendel's first Law: this states that characters are controlled by pairs of genes, and that the genes of each pair segregate from one another during the formation of the germ cells (Fig. 1).

According to Mendel's first Law, half the sex cells of an *AB* person should contain gene *A* and half gene *B*, and from the type of mating shown here half the children should be group *A* and half group *B*. You can see how beautifully the observed figures fit the theory.

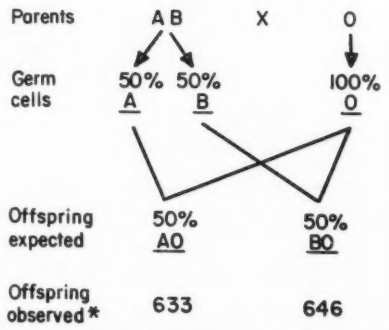


FIGURE 1: ABO groups illustrating Mendel's 1st Law (that of Independent Segregation) collected from the literature by A. S. Wiener[14].

Mendel's second Law, the Law of Inpendent Assortment, states that when two or more pairs of genes segregate simultaneously the distribution of any one of them is independent of the distribution of the others.

Landsteiner and Levine[1], when they established that the *MN* groups were independent of the *ABO* groups, were confirming Mendel's second Law — probably for the first time that this had been done using human material.

A good illustration of the *ABO* and *MNSs* genes independently assorting themselves is to be seen in Fig. 2. The groups show that the quadruplets are all dissimilar: they have arisen from four different ova. The mother's contribution to each child is written first. The ovum from which the child on the left has arisen contained the mother's $A_1$ gene and her *MS*; the second contained her *O* gene and *MS*; the third contained her *O* gene and her *Ns*; while the ovum for the fourth contained her $A_1$ and *Ns*. In other words, the partnership in any one ovum of *A* or of *O* with *M* or with *N* has been entirely a matter of chance.

In Mendel's time the chromosomes had not been discovered so he could not fore-

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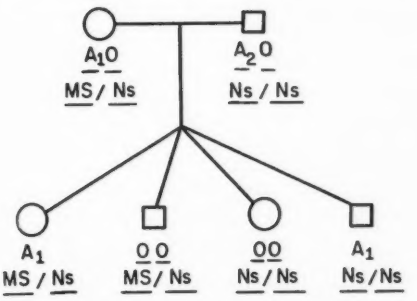


FIGURE 2: ABO and MNSs groups illustrating Mendel's 2nd Law (that of Independent Assortment). The Bellengen, New South Wales, Quadruplets. (After Walsh[11].)

see that his second Law would not always hold. Mendel must have thought of all the genes as being independent of each other — like dots in the nucleoplasm, so that one of each pair of allelic genes was free to enter a germ cell quite independently of which one of all the other pairs entered it.

But when it became known that the genes were carried on chromosomes, it was realized that the destination of a gene could not be independent of the other genes traveling on the same chromosome.

As you know, genes traveling on the same chromosomes are said to be linked and it is this phenomenon of linkage, together with the phenomenon of crossing-over, that was so brilliantly applied, in this country, to the achievement of chromosome maps of *Drosophila* and of some other species. That was in the first quarter of this century; but we still have not got very far with the maps of human chromosomes.

Two difficulties in chromosome mapping in man are, of course, the long interval between generations, and the awkwardness of arranging experimental matings. But probably the main difficulty has been the shortage of normal physiological characters which are inherited in a sufficiently simple way for us to follow. Most normal human characters are complex in their inheritance for they depend on many genes, all of which, individually, no doubt behave in a simple Mendelian way but which, acting together, obscure their individual tracks.

Many rare diseases and abnormalities are inherited in a simple way but they are too rare to be of much use on their own for mapping the chromosomes.

The blood groups are ideal characters for use as chromosome markers. They are simply inherited and are, in general, clearly classifiable and free from doubtful intermediate forms. Further, they tend to be well distributed in a population: blood groups not well distributed are not much use as markers — for example very rare groups like *Levay* are no more use as markers than rare diseases and the same can be said of very common blood groups, such as *Vel.*

The list of markers is shown in Figure 3: these are all normal characters; their inheritance is understood with reasonable certainty and they show sufficient variation to be useful as chromosome markers.

Blood groups and the secretion of blood group antigens in saliva make ten of these 14 characters. So you see, that just for the present, blood groups contribute by far the greater part of our precise knowledge of the inheritance of normal human characters.

The inheritance of the last three characters is less solidly established than that of the others — comparatively few families having yet been tested. Furthermore, the 12th character, the difference between the presence or absence of sickle cell hemoglobin is only of use in a population where the two forms of hemoglobin, sickle and normal, are both common. Therefore its usefulness as a marker character is limited, being confined, I believe, to people of African origin and to certain tribes in South India.

So, these are the surveyors' tools with which to begin this most exciting cartography of the human chromosomes.

Sex-linked genes are fairly easy to detect and several are known. Auto-

NORMAL CHARACTERS THAT MARK 14 POINTS ON THE AUTOSOMES OF MAN

| | | |
|---|---|---|
| 1. | ABO blood groups | 1900 |
| | $A_1A_2$ subdivisions | 1911 |
| 2. | M N blood groups | 1927 |
| | M N S s subdivisions | 1947 |
| 3. | P blood groups | 1927 |
| | $L_1P_2$ subdivisions | 1955 |
| 4. | Ability to taste phenyl thio-carbamide | 1931 |
| 5. | Secretion of the ABO antigens in saliva | 1932 |
| 5. | Rh blood groups | 1940 |
| | Many subsequent subdivisions | |
| 7. | Lutheran blood groups | 1954 |
| 8. | Kell blood groups | 1946 |
| 9. | Lewis blood groups | 1946 |
| | Lewis saliva groups | 1954 |
| 10. | Duffy blood groups | 1950 |
| 11. | Kidd blood groups | 1951 |
| 12. | Hemoglobin A and S | 1947 |
| 13. | Haptoglobins in serum | 1955 |
| 14. | The Gm serum groups | 1956 |

FIGURE 3.

somal linkage, on the other hand, is more difficult to detect. Somewhere on the 22 autosomes are the genes for all the blood groups. We do not know on which pair any of them are, or how many pairs they mark. So far the evidence is that they are quite well spread out over the autosomes; and this is all to the good, for the net is cast the wider for catching linkages.

But, wherever it is situated, each blood group gene is strung amongst hundreds of other genes; and by observing which characters are inherited with which blood groups, the position of more and more of these other genes will gradually be plotted.

I will now try to illustrate this rather difficult subject of linkage with an example. When two genes are fairly close to each other on one chromosome, the characters which they represent may be seen traveling with each other through the two or more generations of the family being studied.

You will know that there is a rare abnormality, due to a dominant gene, in which most of the red cells are oval instead of round. Some of you will have seen such red cells, and a very surprising sight they are—even under low power—if you are not expecting them.

In this pedigree (Figure 4), which is part of a much larger one, you will see

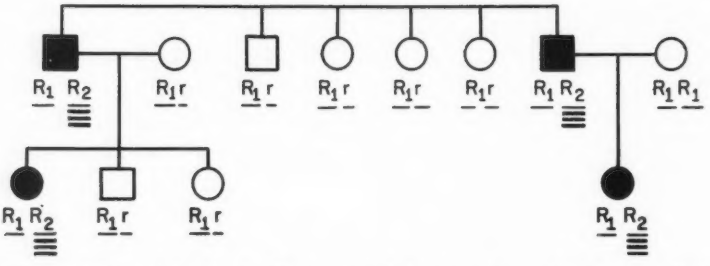


FIGURE 4: Linkage between the Rh genes and the genes for oval red cells. Black=oval cells; White=normal cells. (Goodall, Hendry, Lawler and Stephen[12].)

that the posession of oval cells, marked in black, coincides with the presence of the $R_2$ antigens of the *Rh* system. They are being inherited together. This was not a chance coincidence.

This is what the coincidence of characters was revealing (Figure 5): it showed that the genes for *Rh* and for oval red cells are on the same chromosome pair. In the family we have just seen the arrangement was this—oval gene with $R_2$—but in other families Dr. Lawler[2] has found that the oval gene is attached to *r* and in others to $R_1$, as would be expected.

You may remember that in the formation of the sex cells at meiosis, the two chromosomes of each pair coil around each other and then retract from each other to opposite poles of the spindle. This retreat pulls out the coils, and both chromosomes may break, at the same level, where they cross, and a broken end may then join up with the loose end of the opposite choromosome. This is called crossing-over. If crossing-over happened somewhere between these two genes—say, at the dotted line in the Figure—then two recombinant chromosomes could arise: one carrying the oval gene and $R_1$ and the other carrying the not-oval gene and $R_2$. The previous pedigree showed no example of a recombinant. (I should say that this is a somewhat simplified version of what happens at meiosis.)

Crossing-over occurs more or less at random along the chromosome so that the greater the distance between the two genes, the greater the chance of crossing-over happening between them. So, it follows that we can use the frequency of recombinations between two linked characters as an index of the distance between their two genes.

In Dr. Lawler's families about 10 per cent of the children departed from their particular family alignment, that is to say, 10 per cent were recombinants, and so the distance between the two genes is said to be 10 units.

Another search for linkage made by the Galton Laboratory, in London, has been brilliantly successful. Renwick and

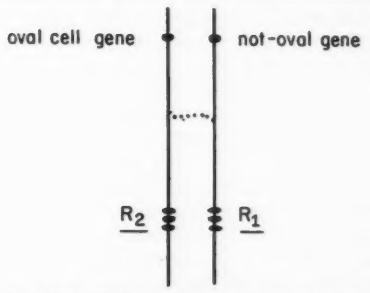


FIGURE 5: Linkage between the genes for oval cells and for Rh. The alignment is that seen in the family shown in the previous slide. In other families the oval cell gene is on the same chromosome as $R_1$, in others as r, et cetera.

Lawler[3] have discovered that the gene responsible for a rare dominant condition called "nail-patella syndrome," or, if you prefer it, "hereditary onycho-osteodysplasia," is on the same chromosome as the *ABO* locus. Six large families showing the abnormality were tested, and the linkage beautifully demonstrated. The recombination fraction again is 10 per cent. So the length of chromosome between the nail patella locus and the *ABO* locus happens to be about the same as that between the oval cell locus and the *Rh* locus.

Figure 6 shows a small part of one of the pedigrees. The point of giving this Figure is that it contains a recombinant. Figure 4, showing the oval cells traveling with *Rh*, did not happen to contain an example of this phenomenon. The part of the pedigree not given here had shown quite clearly that the *ABO* representative traveling with the nail patella gene is, in this family, the gene *O* which

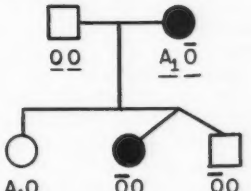


FIGURE 6: AO recombinant. Black=nail patella syndrome; White=normal. (Renwick and Lawler[3].)

is here marked with a bar. The mother in this part of the pedigree has given her $A_1$ chromosome to the first child without the patella gene—which conforms to the family tradition. The girl twin conforms too, for she has received the $O$ chromosome carrying the patella gene. But the boy twin has received an $O$ chromosome from his mother, which, luckily for him, had, during the formation of the ovum, exchanged the part of its length containing the harmful gene for the corresponding part of an $A_1$ extremely common gene which is necessary to prevent red cells being oval.

A summary of the linkages is given in Figure 7. Most of those in the top row are fairly well certain; those in the second row are probable linkages yet to be confirmed.

In an unknown position on the top part of the X we have to make room for another gene — that responsible for the psuedo-hypertrophic type of muscular dystrophy.

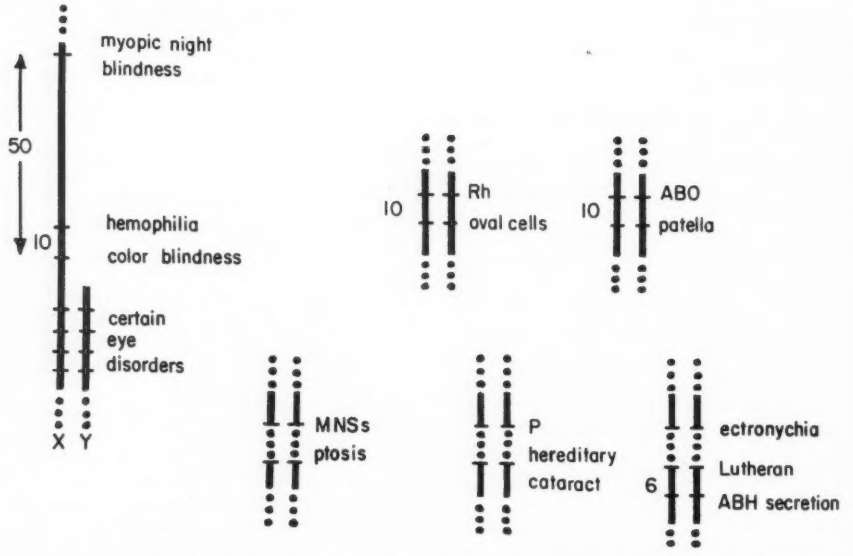


**FIGURE 7: The beginnings of a map of the human chromorsomes. The genes for the 9 remaining marker characters may be on the above chromosomes (not XY): alternatively and more probably they may be on the 17 pairs not shown.**

chromosome, which lacked the abnormal patella gene.

Of course, you may feel that to know the whereabouts of an extremely rare gene which causes miserable patellae is not perhaps illuminating to a degree; but we may reflect that now we know the whereabouts of a very common gene necessary for the development of our own magnificent patellae. In the same way, I can hardly think now of the *Rh* genes without picturing, near them, that

The gene for haemophilia is thought to be about 10 units from the gene for red-green color-blindness — it is not known which is at the top nor is the relative position of the gene for myopic night-blindness known, though it is estimated to be 50 units from the gene for color-blindness. We would not be able to recognize linkage between genes as far apart as 50 units, for since half the gametes would be cross-overs the resulting characters would appear to be as

independent as if their genes were on separate chromosomes. But in this case the genes had to be linked to each other because both were sex-linked.

In the same way, autosomal genes might be on the same chromosome yet be separated by such a distance that crossing-over happened too frequently for linkage to be detectable Ultimately, of course, such linkages will be recognized by the finding of intervening linked genes which will bridge the gap.

The linkage between the *Lutheran* and *secretor* genes is fairly well established and the map distance is estimated as about 6 units. If ectronychia turns out really to be on this chromosome then its place in relation to *secretion* and *Lutheran* will remain to be discovered. It could be north of *Lutheran*, as shown here, it could be between the two or it could be south of *secretion*.

It is only in the last six years that the long and arduous search for autosomal linkage in man has been thus rewarded. Now, with 14 good marker genes, linkages should be found thick and fast and the map of the human chromosomes begin to lose some of its antarctic blankness and soon it should begin to look more like the crowded maps of the four chromosomes of *Drosophilia melanogaster*.

When a reasonably detailed map of the human chromosomes is achieved, what then? Well, of course we cannot possibly foresee what further knowledge will be built on such a foundation; we can only guess at some of the nearer possibilities which are almost within sight.

It would, for example, be useful to be able to recognize the carriers of genes for certain inherited diseases that have their onset later in life. Huntington's chorea and Altzheimer's syndrome are examples of this type of disease. Both are very distressing, but fortunately rare, mental diseases; the first signs occur at an age when the doomed person has had children. As both diseases are dominant characters, half the children will get the disease when their time comes. But there is no way at present of telling which children are doomed. Linkage with marker genes would enable carriers of the genes for such diseases to be recognized early, so that they could avoid having children.

This is the usual example of the usefulness of human chromosome maps. But it always sounds to me a little feeble. A much more important consequence of chromosome maps will, I am sure, be the identification of chromosome abnormalities. No doubt it will be found that some pathological conditions are due to deletions of parts of chromosomes, to inversions and to translocations. Other abnormalities may be due to the presence of only one of a certain pair of chromosomes, or perhaps to the presence of three chromosomes instead of a pair. Such things happen in *Drosophila* and in mice, and so surely must in man. Deletions have, in fact, already been observed in cultures of human tissue. They had been induced by irradiation of the tissue.

Recently we were given a hint of the presence of a chromosomal upheaval when we grouped the blood of a true hermaphrodite, a person in whose abdomen both ovarian and testicular tissue was found. Such people are extremely rare, and the blood, too, was of so rare a kind that it had not at that time been previously reported. It was a case of the antigen *B* being present in the saliva but absent from the red cells. It is difficult to believe that blood so extraordinary finds itself merely by chance in a body so extraordinary in other ways. It is much easier to believe that both conditions are due to one and the same chromosomal upset.

A foretaste of another use of linkage is to be found in its very subtle application, by Renwick and Lawler[4], to diagnosis. The rare inherited peculiarity of the finger nails, which they describe and call by the name of ectronychia, could well have been a variation of the nail patella syndrome. But the absence of linkage between ectronychia and the *ABO* groups showed this abnormality to be fundamentally different in origin from the nail patella condition.

Incidentally, in the normal alleles of

these two rare genes we have come to recognize two very common genes necessary for normal fingernails and, what is more, we nearly know where they are situated.

I have run on for a long time about the present and future contribution of blood groups to the knowledge of human chromosomes because I feel that this is perhaps their most important role in the future. But now I must mention, even though very briefly, some other ways in which the groups have contributed to human genetics.

Of course, erythroblastosis fetalis is a shining example. When the consequences of red cell antigen differences between mother and fetus were first recognized by Levine, Burnham, Katzin and Vogel[5], blood groups thereby made a great and original contribution to genetics as a whole, and not merely to human genetics and medicine.

The earlier work on the complexity of the *Rh* genes should be mentioned too, because in 1944 when Fisher[6] first suggested that a system of closely linked genes, *C, D* and *E,* could best explain the *Rh* interactions, the idea of neighboring genes doing more or less the same job was not generally accepted in genetics. But since that time some fine examples have been found in a variety of species. What Fisher saw was probably happening in *Rh* is now known to happen in mice, in *Drosophila,* and in the mold *Aspergillus nidulans* and, it seems, even in the bacteriophage: it is clearly a common gambit of Nature.

**II. Some Applications**

Blood groups are being used more and more for distinguishing between mono-

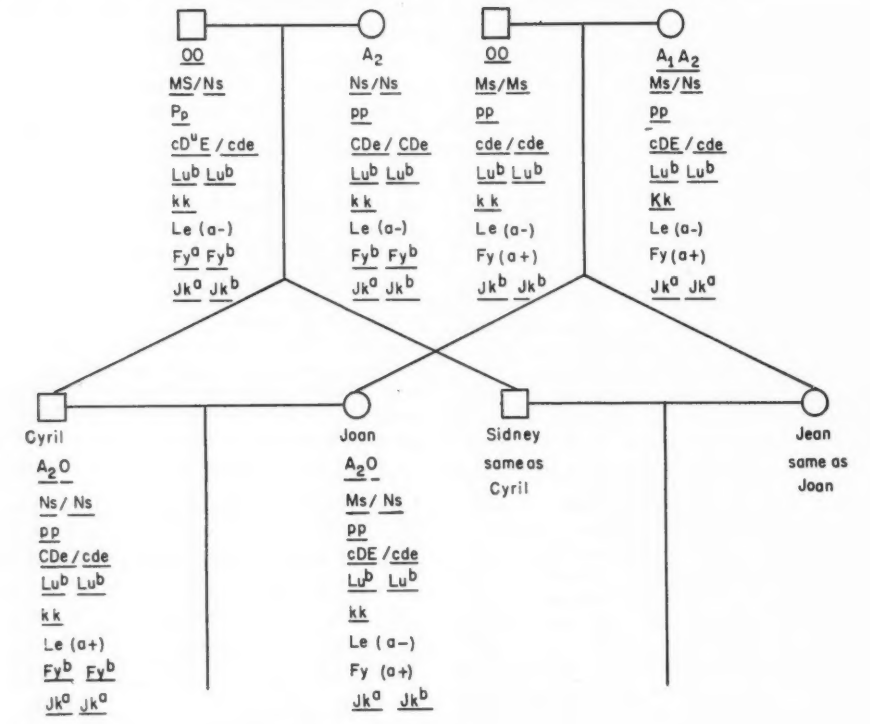


FIGURE 8: Cousins that are sisters.

zygotic and dizygotic twins. Since monozygotic twins can be used as a measure of the effect of environment, freed from the complication of inherited differences, it is important to establish their zygosity.

If any of the blood groups are different the twins are dizygotic and the question is answered; if all the blood groups are the same the problem is not solved, but the probability of the twins being monozygotic or dizygotic can be calculated. When the parents of the twins have been grouped the calculation is relatively simple. When the parents of the twins are not available the calculation is much more difficult, but it need not now be done, for Smith and Penrose[7] have published very convenient tables showing the relative chance in favor of dizygosity for twins showing the same *$A_1A_2BO$, MNSs, P, Lutheran, Kell, Duffy, Kidd* and *secretion* phenotypes.

Figure 8 is a curiosity: identical twins have identical genes and the blood groups helped to prove that the two boy twins, Cyril and Sidney, are indeed identical. The blood groups helped to prove that the two girl twins, Joan and Jean, are also identical. Such a marriage of two pairs of identical twins must be a very rare event in England, where this happened recently, though it is said to be more common in Japan. When we did the blood groups the two girls were pregnant. We hoped their children would be of different sex and would later on want to marry each other. If that should happen both the English Church and the English Law would bless this marriage of cousins, though in biological truth it would be a marriage of brother and sister. However, these hopes have been dashed for the children were both girls.

I would now like to spend a few minutes speaking of the fascinating curiosity of chimeras—dissimilar twins who share each other's blood. Most of you probably know the story and I must ask your indulgence for repeating it.

The story began in 1916 when Lillie[8] published in Science his discovery that, in cattle, blood vessels connected the circulations of dissimilar twin embryos. Lillie realized that in this anastomosis was to be found the explanation of the freemartin condition. As long as cattle have been domesticated it must have been known that the female of a male: female twin pair, is usually sterile. This sterile female is known as a freemartin. Lillie believed, and his views have not been superseded, that the hormones of the bull twin cross the communicating vessels and suppress the proper development of the sex apparatus of the cow twin.

The next big step was made by Owen[9] in 1945. Owen discovered that primordial red cells, having crossed the communicating vessels, could take root in the opposite twin and continue, throughout the life of that animal, to produce red cells stamped with the blood group antigens of its twin.

A cow or bull with such a mixture of blood transmits to the next generation genes only for the truly inherited red cell antigens, not genes for the antigens merely lent for life by the other twin. A cow with mixed blood will not, of course, be a freemartin when her fellow dissimilar twin is a female.

The next step was the discovery that mixtures of blood could happen, as an extreme rarity, in human dissimilar twins. Then the same thing was found as a rarity in sheep. Then it was discovered that dissimilar twin chicks are chimeras—probably to a chick.

Five human chimeras have now been investigated, in England. The first was described in 1953—a woman whose twin brother had died 25 years previously. After a gap of four years two more chimeras were reported, this June.

The blood of all five chimeras has been a mixture of *O* and *$A_1$*. Chimeras with mixtures of blood that did not differ on the *ABO* system might easily escape notice. We devised a method of separating the *O* and *$A_1$* cells and the separated cells could be shown to differ on other systems of groups also.

Figure 9 shows a small part of the pedigree of one of the two complete chimera pairs. The blood group systems

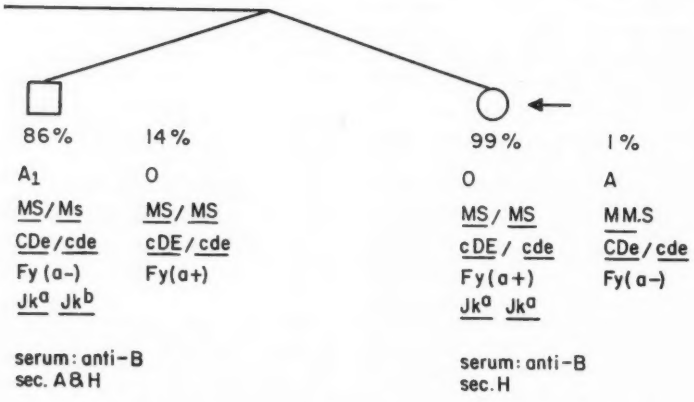


FIGURE 9: Part of the pedigree of Miss Wa. (Booth, Plaut, James, Ikin, Moores, Sanger and Race[13].)

on which the twins do not differ have been left out.

As you will see, the two components in the mixtures differed in their reactions with anti-*A*, anti-*s*, anti-*C* and anti-*E*, anti-$Fy^a$ and anti- $Jk^b$.

We know that the boy twin's *A* series of red cells were truly his own because his saliva contained *A* substance. The *O* series must belong to his sister — and this is confirmed by her saliva containing *H* but no *A*.

Blood films from the male twin were examined by Dr. W. M. Davidson who found some polymorphs to have the drumstick nuclear knobs present normally only in females. The proportion of polymorphs with drumsticks was compatible with a mixture of male and female blood and the proportion indicated by the red cells. It seems then that the ancestors of polymorphs, as well as of red cells, can be successfully grafted in utero.

All three chimeras who are genetically group *O* but who possess grafted *A* cells lack anti-*A*. This is an example of the general phenomenon of acquired tolerance outlined by Burnet[10] and supported by the work of Owen[9]. According to the theory, an animal does not produce antibody to an antigen to which it has been exposed early in fetal life.

All three sets have been brother-sister pairs. Two of the females are married and have three children each, so clearly they are not freemartins. Evidently the human male embryo is backward compared with the bull embryo in hormone production—at least he is if he is an English embryo. It may be different here.

The commonest problem to which the sure knowledge of the manner of inheritance of the blood groups can be applied is, of course, the paternity case. As a rule, blood groups can only exclude paternity: Figure 10 shows how well they could do it at the moment. Of course several of these antibodies would probably not be available at any one laboratory, and we know that several of the systems are too new to be acceptable to the Courts of Law.

So we see that the *ABO* groups alone exclude 17.6 per cent of men falsely accused. The *MNSs* groups are the most efficient, for they exclude 31.6 per cent. *Rh, Duffy* and *Kidd* are all very efficient too. Using all these antisera 78 per cent of wrongfully accused men would be exonerated.

We do not in our Unit do tests for legal purposes, though during the course of our work on the blood groups of families we meet a number of examples of exclusion. The family shown in Figure

The chances of an Englishman being exonerated, by the blood groups, of a false charge of paternity brought by an English woman:

| | *Exclusion by Each System* | *Combined Exclusion* |
|---|---|---|
| 1. ABO | 0.1760 | 0.1760 |
| 2. MNSs | 0.3157 | 0.4361 |
| 3. Rh | 0.2520 | 0.5782 |
| 4. Lutheran | 0.0375 | 0.5940 |
| 5. Kell | 0.0436 | 0.6117 |
| 6. Duffy | 0.2427 | 0.7059 |
| 7. Kidd | 0.2500 | 0.7794 |

1. Schiff and Boyd, *Blood Grouping Technique*, page 153.
2. Calculations by Sir Ronald Fisher, based on the use of antiM, anti-N, anti-S and anti-s and the frequencies given by Race and Sanger, *Blood Groups in Man* (which is also the source of the following frequencies).
3. Calculations by Sir Ronald Fisher, based on the use of anti-C, -c, -D, -E.
4. Based on the use of anti-$Lu^a$ and anti-$Lu^b$.
5. Based on the use of anti-K and anti-k.
6. Based on the use of anti-$Fy^a$ and anti-$Fy^b$.
7. Based on the use of anti-$Jk^a$ and anti-$Jk^b$.

FIGURE 10.

11 was tested years ago, but I could not resist showing it once again because of its very powerful moral. The third child is shown to be extra-marital, for he has *E* that these parents lack; this child stimulated anti-*D* in the mother, so that when the next *Rh* positive child, the fifth child, came along he suffered from hemolytic disease: he was born by Caesarian section and the mother was sterilized. After her sterilization the mother had only one more child, and he was extra-marital for he was group *B*—and neither husband nor wife had a *B* gene—but he was *Rh* negative and so escaped the disease and rather blunted the moral.

Recently we applied blood groups to try and help in what must be a somewhat unusual problem. The two young people in Figure 12 wanted to get married, but the mother of the girl was getting into a very worried state about it because, just before her daughter was born, she had had an affair with the father of the boy, and she feared that the girl and boy might be half-sister and half-brother.

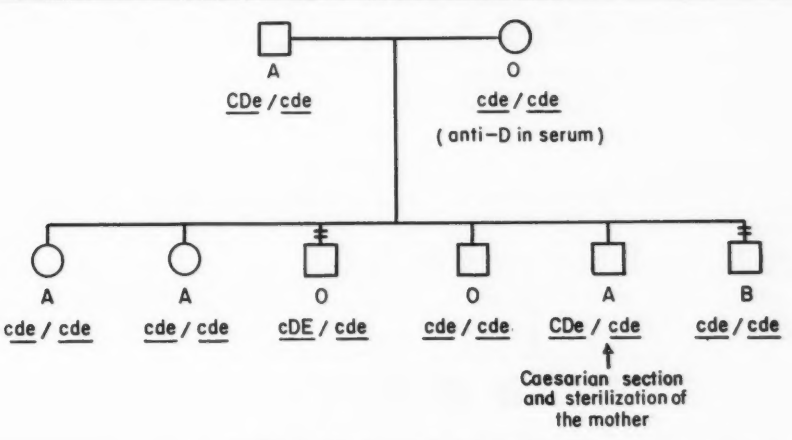


FIGURE 11: Exclusion of paternity.

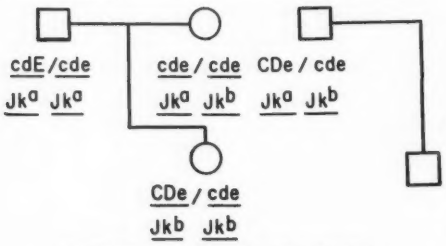


FIGURE 12: Exclusion of paternity.

All the people involved knew of the affair and they felt that the mother was worrying about nothing. The man on the left was sure he was the father of the girl because of likenesses to himself that he could see in her; and the man on the right was sure that he was not the father of the girl because of the precautions he took.

There was no question of legal action following, so we said we would do the groups, fully expecting that the whole family would be made happy by the results. As you see, the results were most unhappy and it would have been better if the tests had never been done. The man on the left is excluded from being the father of the girl by both his *Rh* and his *Kidd* groups. The man on the right could be the father of the girl. Calculating from all the blood groups, most of which are not shown here, he had about twice as much chance of having a child with the girl's groups as had a random man. I am sorry that I do not know the end of the story.

Figure 13 illustrates very well a scientific use of paternity exclusion. The samples were sent to us from what was thought to be one family, but the blood groups showed that this was far from the case.

The two youngest boys are $A_2$ and can-

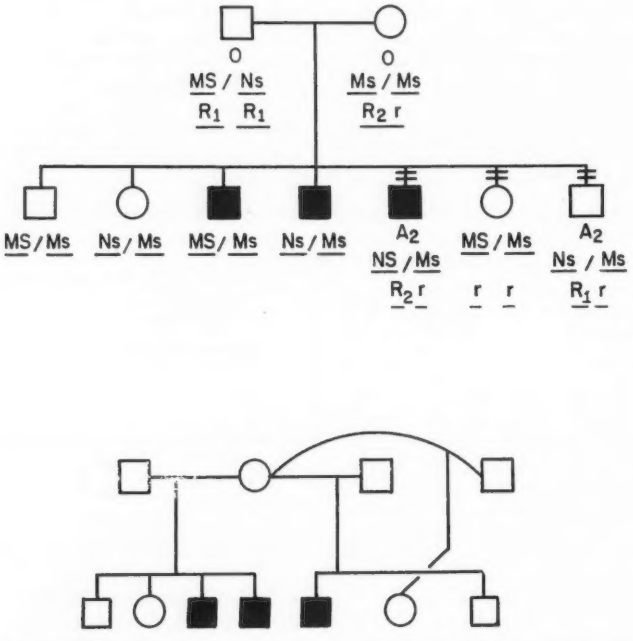


FIGURE 13: Pseudo-hypertrophic muscular dystrophy: a sex-linked recessive condition. (Booth, Plaut, James, Ilkin, Moores, Sanger and Race[13].)

not be the issue of an *O* x *O* mating; the older of the two boys is also shown to be extra-marital by the *Rh* groups, and so is the youngest girl — you see that father of the family has no *r*. These three children require at least two more fathers; they have all received *Ms* from their mother and they could not have received *Ns, Ms and Ns* from one father. The most charitable interpretation is shown above.

The scientific interest lies in the fact that three of the children of the mother have the rare inherited disease, pseudo-hypertrophic muscular dystrophy, here marked in black. The matings of this woman might well have been experimental ones, designed to make clear the manner of inheritance of this disease. The disease is now known to be a sex-linked recessive character, but so much could have been learned from this family alone. Very briefly the reasoning is as follows: the disease is clearly recessive for both parents of the first two affected boys are normal. The disease can hardly be an autosomal recessive, for this would require the abnormal gene to have come from both parents, and it would mean that not only the wife but both the husband and the second mate would all have to be carriers of an extremely rare gene. This is too much to believe, and the only alternative is that the disease is a sex-linked recessive character depending on one gene only, which is being supplied by the mother.

If progress goes on at the present rate, before long, virtual proof of paternity should be a frequent event. At present it is a rare event, but it happens whenever a child is shown to have a very rare antigen which his father also has.

In conclusion, I should say that the use of any of the blood groups in problems of parentage is, of course, dependent on the antisera being available; it should depend also on the tests being done by an expert constantly engaged in such work.

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# WATER AND ELECTROLYTE BALANCE DURING PREGNANCY

SAMUEL J. TURNER, M.D.*

Problems concerned with water and electrolyte balance arise frequently during gestation. Metabolic variations in the maternal organism initiated by the growing uterus and its contents, frequently result in extensive alteration in hormonal, circulatory, renal, gastrointestinal and cerebral physiology. These may lead either to a depletion or retention of water and electrolytes which may seriously interfere with the continuation of a normal pregnancy. It is the purpose of this presentation to discuss some of the more frequent clinicopathologic manifestations complicating pregnancy, in which water and electrolyte balance deserve special consideration.

## BASIC CONSIDERATIONS

The fluid[1,2,3] which normally accounts for 44 to 65 per cent of the weight of an adult female, is categorically distributed into three compartments: (1) intracellular, (2) extracellular: (a) intravascular, (b) interstitial. The intracellular fluid makes up to 35 to 40 per cent, the intravascular fluid accounts for 4 to 5 per cent, and the fluid contained in interstitial spaces accounts for 11 to 15 per cent of the body weight.

The water needs of the body[1,2,4,6] are usually acquired by the intake of water and foods which contain 70 to 90 per cent water; about 300ml.. of water are produced by the metabolism of 2500 calories. Normally, the body regulates the intake of water according to its needs. The normal daily physiologic loss of water consists of 700 to 1000ml. by evaporation from the skin and lungs (insensible loss), 50 to 200ml. with feces and 1000 to 1500ml. as urine. The loss of fluid may be exaggerated in the presence of excessive sweating, increase in respiratory rate, vomiting, diarrhea, suction drainage of the G.I. tract and in renal insufficiency.

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It is generally agreed that there is an increased retention of water by the maternal organism during pregnancy[7a,11,12,14]. Clinically this view can be confirmed by the marked postpartum diuresis, by the simultaneous rapid loss of weight in the early puerperium and by the atonic, flaccid condition of the tissues after diuresis. Retention of water may be caused by the following physiologic factors:

1. [11] An increase in venous pressure of the legs may be produced by the increased intra-abdominal pressure, pressure of the uterus against pelvic veins, placental circulation which resembles an A.V. aneurysm and by gravity. This increase raises the hydrostatic pressure of the capillaries to a level where it approaches or, on standing may even exceed the oncotic (osmotic) pressure leading to increased filtration and diminished capillary reabsorption of fluid in the legs with a resultant accumulation of interstitial fluid. Since the legs constitute 37 per cent of the body weight, a considerable volume of water may be retained. In recumbency some or all of the retained fluid may be eliminated from the body; hence the reason for the relative polynocturia during the latter part of gestation.

2. [7a] The decrease in colloid osmotic pressure of the plasma amounts to approximately 20 per cent during pregnancy. This may be attributed to the drop of approximately 1 gm. of protein per 100ml. of serum. The decrease in serum proteins and the osmotic pressure of plasma along with other factors may be responsible for the retention of interstitial fluid resulting in edema during normal and toxemic pregnancy.

3. Sodium retention[11] occurs throughout the entire course of pregnancy; the total retention per week as calculated by several authors ranged from 1.61 to 8.81gms. Some of the sodium may be stored in an "osmotically inactive" form because the water retained by the body can account for only a fraction of the

positive sodium balance. However, the "osmotically active" sodium no doubt plays an important role in the actual water retained during pregnancy.

4. Hormonal factors bear considerable influence:

(a) Steroidal sex hormones (estrogen and progesterone) are produced by the placenta in large quantities during gestation[7c] and are known to have properties which aid in retention of sodium and water in all fluid compartments.

(b) The adrenal hypertrophy during gestation results in hyperactivity, with a progressive increase in the rate of secretion of most of the corticosteroids. Aldosterone is secreted by the zona glomerulosa and causes sodium retention, potassium excretion and hypertension. Water is also correspondingly retained to equilibrate osmotic pressure of body fluids[7b,13]. Lieberman[8] suggested that glucosteroids may inhibit the action of aldosterone and thus curtail retention of sodium and water. Eastman believes[7b] that a placental factor similar to A.C.T.H. is most likely responsible for the stimulation of the adrenal cortex. A disturbance in placental physiology, through its effect on the production of adrenal hormones, may be one of the major contributing factors in toxemia of pregnancy.

(c) [1, 12, 5a] The antidiuretic hormone with its great sensitivity to variation in osmotic pressure of blood plasma plays a considerable role in urinary output. An elevation in plasma osmotic pressure results in a decrease of urinary output, whereas a drop in plasma osmotic pressure results in increased urinary excretion. Thus in edema of the lower extremities, the recumbent position produces a decrease in venous pressure, readjustment in hydrostatic pressure of arterial capillaries and a return to the plasma of retained water from the lower extremities. This in turn causes a drop in osmotic pressure of blood plasma, a decreased secretion of A.D.H. and polyuria with loss of excess body water.

5. Renal hemodynamics.

The glomerular filtration rate is increased during normal pregnancy and decreased in toxemia[21]. A normal non-pregnant woman consumes 8 to 15gms. of salt in 24 hours which she is able to eliminate. Normally the kidney can concentrate sodium chloride up to 2 per cent in the urine. During pregnancy the renal tubules are not able to concentrate to such an extent and require a larger urinary output to eliminate the sodium not normally needed by the body[22]. Even an extremely small variation in the delicate glomerular-tubular balance may result in retention of sodium and water. In cool weater, a smaller amount of water may be ingested and in hot weather, excessive perspiration may occur. In either event, less water will be delivered to the kidney for adequate excretion of sodium. The retained salt consequently binds a proportionate amount of water to cause edema and disturbance in cellular metabolism.

6. Other factors.

The rate of sweating and the content of sodium in the sweat is lower in normal and toxemic pregnant women than in normal non-pregnant women. The concentration of sodium in the saliva was found to be higher in normal non-pregnant than in normal and toxemic pregnant subjects[22]. The tendency for retention of sodium by the sweat and salivary glands is a further demonstration of the abnormality of water and electrolyte metabolism during pregnancy. This is believed to be due to an over-production of adrenal corticosteroids.

In an extensive study, Chesley[11] estimated 6.3 liters (13.85 pounds) of water as the average retention during normal pregnancy; the calculated allocation was 2.9 pounds for plasma, 5.8 pounds for the interstitial spaces, 1.6 pounds for the new tissue in the uterus and breasts and the remainder of 3.3 to 4 pounds for the products of conception. It was shown by measurements of thiocyanate available water, that the water loss from the im-

mediate antepartum period until 6 weeks postpartum is in close agreement with the total available water gained during gestation.

Water and electrolyte imbalance is an important feature in nausea and vomiting of pregnancy, prolonged labor, edema of normal pregnancy and in toxemia of pregnancy.

**Nausea and Vomiting of Pregnancy**[7, 15]

Nausea and vomiting is the most frequent complication during the first trimester of pregnancy. 50 to 60 per cent of pregnant women experience nausea, 15-20 per cent have vomiting and less than 1 per cent develop hyperemesis gravidarum. The milder forms are best treated by gaining the patient's confidence, by administration of mild sedatives, antiemetics, multiple vitamins and by adequate rest with prescription of small appetizing meals every 2 or 3 hours during waking hours. The management has to be directed towards prevention of dehydration and weight loss. With this type of approach hospitalization may become necessary in less than one in every 300 pregnancies. Eastman[7e] hospitalized 120 patients during the past 20 years; all of the patients recovered; none of them had to be aborted. My own experience with hyperemesis gravidarum which required hospitalization for pernicious and intractable vomiting consists of 5 patients during the past 12 years who recovered without any need for interruption of pregnancy.

The clinical features of severe hyperemesis gravidarum include evidence of dehydration with intractable vomiting, weakness, dizziness and thirst. Objectively, there may be a shrinking, wrinkling and dryness of the tongue; temperature elevation, tachycardia and increase in respiratory rate may also be present. Laboratory studies may disclose hemoconcentration, elevated hematocrit reading, slight decrease in blood chlorides and potassium, decreased $CO_2$ combining power with a drop in serum pH. There may be an oliguria with the presence of ketonuria which is a result of increased fat metabolism.

The treatment must be directed towards re-establishment of water, electrolyte and acid-base balance. Intravenous fluids containing 5 per cent glucose in physiologic saline with multiple vitamins should be administered in adequate amounts until the patient is able to tolerate food orally. Electrolyte and pH determinations should be done as necessary for proper guidance of treatment. Potassium may be administered as needed if the patient has adequate urinary output. Once electrolyte balance and pH of plasma is restored to normal limits, recovery of the patient is reasonably assured.

**Prolonged Labor**

Loss of body fluids occurs through sweating, vomiting or non-absorption of fluid from the gastrointestinal tract. Even without clinical signs of dehydration, a marked fall in plasma water occurs after 20 hours of labor. Hawkins and Nixon[16] believe that when signs of dehydration are present, a serious loss of the patient's fluid reserve can be inferred. They observed that after 20 hours of labor, plasma chloride was lower, sodium was elevated and potassium was lower. Fall of potassium in plasma may contribute to uterine inertia. A drop in total circulating eosinophiles may be explained by hyperactivity of the adrenals brought about by the stress of labor. Ketonuria is frequently found because of incomplete combustion of fat associated with starvation and stress. It is therefore advisable to provide adequate amounts of intravenous fluids and electrolytes after 20 hours of labor without waiting for signs of dehydration. 1000 or 2000ml. of 5 per cent glucose in water or isotonic saline with multiple vitamins should be administered intravenously.. After 48 hours of labor, biochemical studies of blood plasma should be done. The fluid reserve of the patient deserves special attention in hot and humid weather or during excessive vomiting.

**Edema of Normal Pregnancy**[7a,9,11,12,14]

Generalized edema or accumulation of excess water and electrolytes in interstitial tissues occurs when the kidneys are not able to excrete an adequate

amount of fluid. Occasionally edema may occur because of a disturbance in hemodynamics in a specific part of the body, resulting in localized edema.

During pregnancy there is an abnormality of water and electrolyte metabolism with retention of water and sodium. It is, therefore, conceivable that even the slightest alteration in the so-called normal physiology may be enough to cause further retention of water and electrolyte in the interstitial tissue to result in occult or visible edema. An increase in capillary hydrosatic pressure causes a dependent edema of the lower extremitieis without albuminuria and hypertension in approximately 75 per cent of all pregnant women during the third trimester. During warm weather, edema may be more pronounced because of increased peripheral vasodilatation. This type of edema usually disappears in a recumbent position; however, when it is still present on arising in the morning then it may be a precursor of the more marked retention of fluids which characterizes toxemia of pregnancy.

**Pre-Eclampsia and Eclampsia**[7, 11, 12 14]

The same predisposing factors responsible for retention of water and electrolytes during normal pregnancy may appear in an exaggerated form to produce pre-eclampsia or eclampsia. Even though the exact mechanism for the excess retention of fluid is not known, it is generaly agreed that it occurs because of a disturbed mechanism of the renal excretory function. Hyperactivity of placental, adrenal cortical and posterior pituitary hormones is believed to produce a disturbance in renal physiology which is associated with excess retention of sodium and water with increased excretion of potassium. Oliguria or anuria and edema soon occur, with results of marked disturbance in cellular metabolism and essential hypertension, albuminuria, convulsions and coma.

Most authorities agree that water and electrolyte metabolism are intimately involved in the pathogenesis of pre-eclampsia and eclampsia. Dieckmann[14a] believed that toxemia of pregnancy is due to an abnormal water and electrolyte balance and that the hypertension and proteinuria were secondary and/or protective in nature; this author also refers to patients with two kinds of true pre-eclampsia—eclampsia: (1) the patient who gains weight, 600 or more grams per week for a period of several weeks, usually shows evidence of considerable retention of water and electrolytes (by edema and/or by marked antepartum weight changes): (2) the patient whose weight is not remarkable and who has little or no edema but who has retained an abnormal amount of sodium which has replaced intracellular potassium with its pathologic results. Snoeck and Pirson[12] believe that water retention is most likely primary in the pathogenesis of eclampsia. Since edema may be associated with cellular dehydration or intracellular water retention, enough disturbance in cellular metabolism to produce the subsequent manifestations of toxemia of pregnancy may occur. Wylie[20] considers alteration in renal circulation as the primary factor of pre-eclampsia-eclampsia; retention of water and electrolytes with edema of the renal parenchyma is given as one of the causes for interference with renal circulation. Renal hypoxia is followed by elaboration of a substance which causes vasoconstriction of the peripheral vascular system which ultimately may lead to severe toxemia.

Whether toxemia of pregnancy is initiated by altered renal circulation from increased pressure against the renal tissue, by uterine-placental ischemia from increase in intrauterine pressure, by the various changes in metabolism of hormones produced by the placenta, the adrenal cortex or the posterior pituitary gland, the end results are the same; namely: excess gain in weight, edema, hypertension, proteinuria with ultimate other clinical manifestations with or without convulsions and coma. Occult edema is perhaps the earliest apparent clinical manifestation. Dieckmann[17] detected significant gain in weight between the 13th and 20 week gestation in patients who subsequently developed pre-ecalampsia. Regardless of the primary cause, our present day knowledge indicates that

toxemia may be best prevented during the antenatal period[18] if a low salt diet and enough water (3000 to 4000ml. daily) is consumed to provide an adequate urinary output. Particular attention should be given to excess gain in weight, edema, blood pressure elevation, proteinuria, anemia, urinary output and blood chemical studies which may be significant in the evaluation of toxemia of pregnancy.

Demonstrable edema or gain in weight of more than one pound a week for several weeks may be considered as excessive retention of water and sodium. Since this is most likely a manifestation of toxemia, all efforts must be directed towards correcting this abnormality. In case of edema involving the lower extremities, a restriction of salt intake and bed rest for 24 to 48 hours is usually sufficient. If there is either occult or evident generalized edema, a diuretic[9] should be given in addition to salt restriction and bed rest. Ammonium chloride, an acidifying agent, 8 to 12 gms. daily may be given for 3 to 4 days. Rolicton® inhibits the reabsorption of sodium and water by the distal renal tubules and may be used for several days by taking 400mgms. taken 2 to 4 times daily. Diamox® is a carbonic anhydrase inhibitor and gives best results when given in one 250mgm. dose in the morning for a period of 3 to 5 days.

All of these diuretics become ineffective after 3 to 4 days. Diuril® remains an effective diuretic for a longer period of time and good results can be obtained with 0.5gm. two times daily[19]. Mercurial diuretics such as mercuhydrin may be used with safety in toxemia of pregnancy if other diuretics fail. In more severe pre-eclampsia with an associated oliguria an osmotic diuretic should be used. Dieckmann[14] recommends 500 to 1000ml. of 20 per cent solution of glucose to be given intravenously over a period of 30 to 50 minutes; the injection could be repeated every 6 to 8 hours to promote adequate urinary output. Glucose is used in severe pre-eclampsia for the abstraction of fluid from the tissues into the circulation in order to overcome the decrease in blood volume and to promote dilution of the concentrated blood elements. Dieckmann has stated that this will result in a diminution in the brain volume, thereby decreasing the tendency for cerebral irritation and convulsions and favoring a return to consciousness. An increase in urinary output occurs during hemodilution, aiding in elimination of excess water and electrolytes from the body. Smaller amounts of 30 to 50 per cent solution of glucose may be given when there is evidence of pulmonary edema. All other means which are usually employed to control hypertension, coma and convulsions should be administered as needed.

**Summary and Conclusions**

1. One can hardly overemphasize the fact that a basic understanding of the alteration of water and electrolyte metabolism brought about by gestation is essential for the proper management of the pregnant woman.

2. During the first trimester marked depletion of water and electrolytes may occur as a result of nausea and vomiting of pregnancy. Comparable problems may arise because of excessive vomiting or sweating during prolonged labor. Regardless of the underlying cause, restitution of adequate body fluids usually provides satisfactory results.

3. The marked increase in hormonal activity stimulated by the placental, adrenal cortical, and posterior pituitary glands effects renal functions so that the kidneys are unable to eliminate all of the water and electrolytes consumed. A retention of water and electrolytes is a manifestation which occurs even in normal pregnancy.

4. The same factors which cause so-called normal retention of water and sodium undoubdtely are also responsible for the excess retention which manifests itself by excessive gain in weight and/or edema which may terminate with a pre-eclampsia-eclampsia syndrome.

5. Immediate attempts to eliminate the edema and excess gain in weight with bed rest, restriction of salt and adminis-

tration of diuretics may bring satisfactory results. Once pre-eclampsia develops, all medical efforts should be undertaken to control the advance of the malady, but termination of pregnancy is the only satisfactory treatment.

6. One must be aware that a gain of more than one pound per week for several successive weeks, or that the appearance of even a mild edema means excess retention of water and electrolytes. These may be signs of an early phase of pre-eclampsia and by energetic therapy, many severe toxemias may be avoided with a better outcome for the mother and baby.

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# THE PRINCIPLES OF PRE AND POSTOPERATIVE MANAGEMENT IN COLON SURGERY

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The goal of pre and postoperative care is to bring the patient to as near a physiologic state as possible prior to surgery and to maintain him that way during operation and afterward, in order to insure a successful outcome. Patients who are well prepared and cared for before, during, and after operation undergo minimal risks, and fewer complications thus enabling them to return to normal rapidly and enabling the surgeon to expand the scope of his procedures.

A complete history, thorough physical examination (including digital and proctoscopic procedures), and performance of necessary laboratory tests are of prime importance. These procedures make possible the establishment of a reasonably correct diagnosis and planning of proper surgical procedure as well as the type of anesthesia. The cardiovascular, respiratory and urinary systems are evaluated. If heart failure or myocardial infarction is present, treatment must be instituted prior to surgery. Pulmonary function may be grossly determined at the time of fluoroscopy.[1] It is also well to remember that dyspnea may occur with depleted blood volume and anemia. An evaluation of the urinary system is necessary because if prostatic hypertrophy with urinary retention is present, placement of an indwelling catheter or prostatectomy prior to the colon procedure should be considered. Electrocardiogram, chest X-ray, barium enema, urinalysis, blood urea nitrogen, prothrombin time, complete blood count, hematocrit and blood volume studies are the minimal examinations which should be performed, provided urgent surgery is not required and there is adequate time for preparation of the patient.

The blood volume should be restored to normal prior to surgery by transfusions, and any blood loss during operation should be replaced. Evans Blue Dye (T-1824), radioactive isotopes or a simple estimation[2] may be made to determine the amount of blood required. It must be kept in mind that the blood volume may be diminished in spite of a normal blood count and hematocrit readings, particularly in patients who have lost weight due to their disease. Nutritional deficiencies and electrolytes should be corrected by attention to diet and infusions.[3,4] Large doses of vitamin C (1000 mgm. daily) should be administered before and after operation to promote good wound healing. Members of the vitamin B complex are required for adequate carbohydrate metabolism. If a prothrombin deficiency is noted, vitamin K should be given.

The history and physical examination will give important information which may aid in preventing postoperative complications. For example, one may wish to wrap the lower limbs with elastic bandages if the patient has severe varicose veins or has had thrombophlebitis or pulmonary embolism. Many patients have received steroid therapy. If these drugs, particular cortisone, were taken in the year before surgery they should be administered before and after operation,[5] since it has been observed that there may be decreased resistance to stress because of adrenal atrophy. Patients who have been receiving reserpine should have the drug stopped at least one week before surgery if possible, because of the danger of hypotension developing during anesthesia and postoperatively. Thus severe postoperative shock and death may be avoided.

The patient should be prepared psychically for the procedure to be performed. The surgeon should discuss the case with the patient to explain the preoperative management, surgery, and further treatment. If the patient requires an ileostomy or colostomy, this should be explained thoroughly, including details of management. This will tend to allay fears and wrong feelings which may

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have been transmitted to the patient by hearsay or acquaintance with someone who has had a colostomy or ileostomy.[6]

In preparing the large bowel for surgery, there are two basic principles which have aided considerably in reducing the mortality to a minimal level (2—4%) enabling open anastomoses to be performed. The first is to eliminate as much of the feces as possible. This is accomplished by mechanical cleansing (enemas) and cathartics (castor oil, magnesium sulfate, phosphosoda, etc.) when there is no contraindication. In addition, a low residue or nonresidue diet is prescribed to further reduce the fecal content, since bacteria comprise about 50% of the solid material in the large bowel. Therefore, after the fecal content has been reduced to a minimum, the second basic principle is to further reduce the bacterial content by means of chemotherapy or antibiotics. Sulfa drugs which are poorly absorbed from the gastrointestinal tract such as sulfasuxidine or sulfathalidine have been utilized. Sulfasuxidine is laxative and aids in liquifying the stool to diminish the fecal content of the bowel. No instances of postoperative staphylococcic enterocolitis have been observed with the use of these sulfa drugs alone. Various investigators have employed these drugs alone, in combination with antibiotics, or antibiotics alone or in combination.

Neomycin without other drugs is our choice as the best agent in preparing the bowel for surgery[7] for several reasons. The healing of the sutured bowel appears to be accelerated, the colon is contracted and the mucosa is not irritated—a desirable situation in large bowel surgery.[8] Neomycin is superior to the sulfa drugs as they tend to make the stool gummy and adherent to the wall of the colon and do not give as good sterilization as neomycin; in addition they require a longer period of preparation. Mucosal ulcerations, particularly about the suture line, and interference with the postoperative return of the flora have been noted with the use of the tetracycline drugs. This enhances the possibility of staphylococcic enterocolitis. Neomycin allows the flora to return in a satisfactory manner. Antibiotics are not given postoperatively when neomycin has been employed unless specifically indicated because there is danger of enterocolitis and the duration of intestinal sterility is not increased.[9] Since neomycin in itself will not liquify the stools, phospho-soda (1 teaspoon twice daily) and a low residue diet is prescribed for one week prior to surgery. One gram of neomycin sulfate is given hourly for four doses and then one gram every four hours until a total of 9 or 10 grams has been administered. The neomycin is first administered 36-48 hours before surgery, as it is desirable to have the patient have an adequate night's sleep before operation. A sodium bicarbonate enema is given the night before operation. A Levin tube is inserted either the evening before or the morning of operation. One gram of a 1 per cent neomycin solution may be instilled in the peritoneal cavity when there has been no time to prepare the bowel and emergency surgery is required. Larger doses of intraperitoneal neomycin have been subject to criticism because of tendency toward respiratory depression. This problem is now under investigation.

Some surgeons consider the prescribing of drugs preparatory to anesthesia as part of the anesthetist's function. However, properly, this should be a joint responsibility of surgeon and anesthetist.

A barbiturate is usually given the night before operation in order to insure a good night's sleep. This is usually administered orally. An antihistamine drug such as phenergan is frequently prescribed. Such drugs tend to potentiate the action of other medicaments without materially increasing respiratory depression. Morphine or demerol should be utilized when pain is present to reduce the amount of anesthesia required and enable smoother induction. Scopolamine or atropine is also given with the narcotic to dry secretions and for the cardiac vagolytic effect. The doses of these drugs will vary with age, fever, excitement, hyperthyroidism, height, weight, etc., and should always be individualized.

Following the surgical procedure the

patient is taken to the recovery room. Several excellent volumes covering this phase of postoperative treatment have been published.[10, 11]

The anesthesia record is referred to in determining the type and further amount of parenteral therapy required. Continuous aspiration of the Levin tube is resumed. The patient is turned frequently and encouraged to cough up mucous. Body heat is conserved. Oxygen therapy is available if needed. In patients who do not expectorate well, carbon dioxide inhalations, endotracheal aspirations or bronchoscopy can be employed. The purpose of this is the prevention of postoperative atelectasis. The fluid intake and output is charted. If a patient has a urinary output of 1,000 cc. or more, he is presumed to be in fluid balance. Frequent blood pressure and pulse readings are taken as well as frequent inspection for bleeding. If the patient does not have a retention catheter and has not voided for a period of 8-10 hours, he is catheterized. The patient is retained in the recovery ward until all vital processes have been restored to a physiologic state. The duration of this stay varies depending upon the patient's disease and the magnitude of the surgical procedure.

On the first postoperative day the patient is ambulated. The Levin tube suction is continued and intravenous alimentation including vitamins and necessary elements, such as potassium, is prescribed. In older patients our procedure has been to keep them slightly dehydrated since they tend to retain fluid and salt to a higher degree during the first 24-48 hours postoperatively. Generally, we limit our fluids in these patients to 2500 cc. daily with a minimum of salt. Narcotics are administered for pain in proper amounts, smaller doses for the elderly. This regimen is continued until the patient is able to take nourishment by mouth. The period of ileus is usually 72 hours after which time bowel sounds may be heard or the patient has passed gas. The Levin tube is removed and the patient is given a diet of surgical liquids. If this is tolerated, he is placed on a low residue diet for two to three days and then on a soft diet.[12, 13, 14, 15] After a week or ten days he may be placed on a regular diet. If there is a permanent colostomy a special diet (to reduce excess gas and diarrhea) must be prescribed while first gaining control and any time later when loose bowel movements occur. After a period of approximately two weeks other foods are then added. If control is still effective two months later, additional foods are prescribed. The purpose of the diet is to assure a formed, solid stool.

Complications must be watched for and promptly treated during the postoperative period. Pulmonary complications usually occur during the first 24 hours. The renal, cardiac, and gastrointestinal systems must be observed. Surgical shock, hiccough, thrombosis, embolism, wound infection, evisceration and sepsis are among the many complications which may occur in the postoperative period. A colostomy may be opened within 48 hours after operation, which is the time when the colon has sealed to the peritoneum. The wound dressing is generally not inspected for one week unless there is a specific indication. Skin sutures may be removed in about a week. A spontaneous bowel movement will usually occur on the fourth or fifth postoperative day. If not, mineral oil may be prescribed. A glycerine suppository may also be effective. Enemas are usually reserved for a later phase of the management.

In cases who have had abdomino-perineal resection of the rectum there is a cavity in the hollow of the sacrum, which has been drained or packed if not closed by primary suture. Removal of the gauze can be started on the third or fourth day. Drains should be advanced and can be removed by the sixth of seventh day. The wound may be irrigated. Drainage of the bladder is usually necessary and may have to be continued for 8 to 10 days, and in some instances where the patient is unable to void for a longer period of time.

Patients who have a permanent ileostomy may require special attention. The care during the first week is essentially the same as that required for a permanent colostomy. The skin may need pro-

tection from ileal discharges. This is accomplished with an ointment or paste. Plastic material or wax paper through which the ileal stoma projects will protect the skin and the contents can be removed by suction or in a basin. These patients may require meticulous care during the early postoperative period in that they are prone to have electrolyte and fluid imbalance. As soon as possible, an adequate diet should be given by mouth. These patients may require some type of bag to collect the secretions. Digital dilatation or irrigation by means of a catheter may have to be employed during the early postoperative period for mild obstructive symptoms.

Upon discharge from the hospital, patients with a permanent colostomy are given instructions as to the care of the colostomy. The colostomy may have to be covered with a gauze dressing or soft absorbent paper in order to collect the small amount of mucous which may escape. These are covered with oiled silk or rubber and held in place by an elastic belt, corset or girdle. The colostomy will have to be irrigated and in a few months time, this will be necessary only about three times a week. Many patients are advised to do some type of exercise during the morning. The patient is assured he is not a cripple—he merely has his opening for evacuation located in a different place where it can be seen, is kept cleaner and obtains better attention. A colostomy is a small price to pay for being alive and well.

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# CHYLOTHORAX DUE TO RETICULUM CELL SARCOMA*

## (Report of a case diagnosed with the aid of a coal tar dye)

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### Introduction

A review of the literature of chylous ascites and chylothorax, as cited by Lyter[1], up to 1900, revealed two cases due to malignant lymphoma and five cases due to carcinoma of the pleura. In 1913, the total number of cases of chylothorax due to all causes was 51 and by 1944, 102 cases had been collected. Nix *et al.*[2], in reviewing the literature to July, 1937, cited a total of 22 cases of chylothorax due to neoplasm and 19 additional cases associated with chylous ascites.

It is the purpose of this paper to report an additional case of chylothorax due to neoplasm, in which the diagnosis was aided by the use of lipophilic coal tar dye. The dye technique employed was that described by Klepser and Berry[3].

*History*:

The thoracic duct was first discovered in the horse by Eustachius (1565), in dogs and other species by Asellius (1622) and in man by Veslinguis in 1634. Chylothorax was first described as a clinical entity by Bartolet in 1633, as cited by Olsen and Wilson[4]. Blalock *et al.*, (1936) succeeded in producing chylothorax experimentally in dogs and cats by ligating the superior vena cava, although Lee[6] had previously shown (1922) that chylous fluid rarely formed from occlusion of the thoracic duct alone. It would appear that the extent of the lymphatic supply, the pathway of collaterals, and the level and completeness of the obstruction are additional factors which determine whether chylothorax will develop.

Lipophilic dyes have been used to demonstrate the chylous nature of chylothorax since 1917. Pisek[8], in that year used Sudan III in a nine week old infant. Fletcher and Harrison[9] also applied this dye to the diagnosis of chyluria in a 17 year old girl with a fistula due to chronic tuberculous peritonitis. They used Sudan III orally and recovered the dye from the urine by ether extraction. Merrill[10] employed aqueous Evans Blue dye injected subcutaneously in the lower limbs in two patients, to visualize the thoracic duct during surgery. It is of value because of the short latency between injection and appearance in the thoracic duct. However, as an aid to the diagnosis of chylothorax, water soluble dyes are of no value, since they can also be found in non-chylous effusions. Vegetable dyes are also valueless as they are destroyed in the stomach. In 1954, Klepser and Berry[3] introduced the use of coal tar dyes which are non-toxic in the doses used. When administered orally with fatty foods they are found only in chylous effusions. The method is simple, cheap and specific and should be used in all cases of turbid, sterile, alkaline pleural fluid which tends to recur after thoracentesis. The only other case of the use of coal tar dye was reported by Garamella[11] in 1958, in a case of traumatic chylothorax; within 40 minutes, coloration of the chest catheter drainage was noted.

*Case Report*

This 66 year old white female was admitted to Mount Sinai Hospital on seven occasions. The first four hospitalizations were between January 1955, and March 1957, because of apparent heart failure manifested by exertional dyspnea, some degree of orthopnea, occasional ankle edema and intermittent auricular fibrillation. In addition, there were several episodes of upper respiratory infections and manifestations of thyrotoxicosis. Hyperthyroidism was treated first with propylthiouracil. In March 1955, she had a subtotal thyroidectomy at the Mayo Clinic followed by an uneventful recov-

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ery. She has received digitalis, quinidine, and mercurials intermittently for several years.

Laboratory examinations performed during the first four admissions were essentially within normal limits except for an elevated sedimentation rate (40 mm.) and a basal metabolic rate of +69%. The PBI and radioactive iodine "uptake" results were consistent with euthyroid state. In March 1957, X-ray revealed an enlarged heart and presence of fluid in the right costophrenic angle with congestion in the left base. The electrocardiogram was interpreted as "abnormal, nonspecific."

On the fifth admission, in June, 1957, she appeared amaciated, but in no acute distress. BP 160/80, pulse 90 and irregular. Respirations were 24 per minute and regular. There was slight cyanosis of the lips and fingernails. Neck veins were slightly engorged and the venous pressure in the left arm was 85 mm. of water, rising to 110 mm. with hepatic pressure. The decholin circulation time was 10 seconds. The heart was slightly enlarged to the left on percussion, and the apical rate was 90 and irregular. Heart tones were of good quality and intensity. At the left lung base posteriorly there was extensive dullness, diminished breath sounds and decreased tactile fremitus. There were no adventitious sounds. The liver was palpated 6 cm. below the right costal margin. There was no tenderness or nodularity. The hepato-jugular reflux was positive. There was no splenomegaly and no abdominal masses were palpated. Examination showed no signs of ascites, peripheral edema or neurological defect.

She was again treated with digitalis and quinidine, with some response, but the cough and dyspnea persisted. On July 5, 1957 a left thoracentesis yielded 600 cc. of milky fluid (Fig. 1) followed by temporary improvement in respiration. When dyspnea reappeared on July 15, another thoracentesis was performed on the left, and 1000 cc. of milky fluid was obtained. A portion of this fluid was mixed with ether and the milky fluid became translucent. A search for the underlying cause of this apparent chylothorax

**FIGURE 1. A comparison of chylous fluid (1) before and (2) after the administration of fat soluble coal tar dye (D & C #6)**

revealed several small firm bilateral supraclavicular lymph nodes, and a few days later, a right supraclavicular node was biopsied. This was reported as malignant lymphoma of reticulum cell type. A needle biopsy of the pleura yielded too little pleura for analysis. On July 19 she was fed one gram of D & C #6 green lipstick dye mixed in one-quarter pound of butter, spread on a slice of bread. Eighteen hours later, this dye was recovered in the thoracentesis fluid (Fig. 1). When ether was added, the green color was extracted in the ether layer.

During this hospitalization, 8 thoracenteses were performed on the left, with a total of 3500 cc. of chylous fluid removed. Several attempts at thoracentesis on the right were unsuccessful. After a short course of oral prednisone and intravenous nitrogen mustard, there was some improvement in appetite and strength. Dyspnea had diminished and the patient was discharged on August 22, 1957.

She was readmitted on September 4, 1957, because of increasing shortness of breath and recurrent left pleural effusion. Again, repeated thoracenteses yielded milky white fluid. On September 17, 9 mg. of nitrogen mustard was introduced into

**FIGURE 2. Chest X-ray at the time diagnosis of chylothorax was established. There is evidence of a left sided effusion.**

the left pleural cavity and this was followed by a course of X-ray treatment to the upper half of the thorax, with a total dose of 3000 roentgen units. After September 17, chest taps were no longer necessary. She was discharged as markedly improved on October 17, 1957,

She remained well at home during the winter of 1957 and was readmitted on April 17, 1958 complaining of recent onset of exertional dyspnea, orthopnea, nausea, vomiting, anorexia, weight loss, abdominal distention and ankle swelling. There was no evidence of fluid reaccumulation on chest examination, although there was dullness, diminished respiration, crepitant rales and bronchial breathing over the right lower lobe. The liver was still enlarged and in addition, a large mass was palpated to the left of the umbilicus, extending into the left upper quadrant of the abdomen. There was shifting dullness and a fluid wave, and 3+ pitting ankle edema. The venous pressure was 52 mm. of water with no rise after hepatic pressure. The decholin circulation time was 10 seconds. A thoracentesis was attempted on the right, but was again unsuccessful. The edema subsided after mercurial diruetics. On April 21, 1958 another intravenous course of nitrogen mustard was given. Other treatment included digitalis and one unit of packed red cells. She was discharged

**FIGURE 3. Chest X-ray seven months after therapy. There is no evidence of reaccumulation of fluid.**

on April 30, 1958, in a satisfactory condition.

Laboratory examinations during the last three admissions revealed hemoglobin values of 10.8 Gm.% (October 1957) and 8.3 Gm.% (April 1958) with normocytic anemia present on both occasions. Serum alkaline phosphatase was 5.6 Bodansky units (June, 1957) and 6.5 units (April, 1958) and there was 46% retention of bromsulfalein in April 1958, while other liver function tests were within normal limits. Analysis of the chylous fluid revealed milky color, alkaline reaction (litmus paper), specific gravity 1.013, total fat content 0.53%, total proteins 3.1%, total solids 5.8%. A smear from the chylous fluid and stained with Sudan III was positive for fat. X-ray films: (See Figs. 2 and 3). E.C.G. was again abnormal, non-specific.

## Discussion

In reviewing the literature on chylothorax, one is struck by the greater incidence of cases reported as secondary to trauma. Nix[2], in his review of 302 cases of chylothorax and chylous ascites cited 123 cases of chylothorax, 146 cases of chylous ascites and 33 cases of combined chylous ascites and chylothorax due to trauma. Included with traumatic chylothorax, are injuries to the thoracic duct during thoracic surgical procedures such as cardiopulmonary surgery, mediastinal explorations and thoracic sympathec-

tomy. Recently, one case has been reported to result from scalene node biopsy[13]. This is understandable when one considers, that in some individuals the thoracic duct extends 5.5 cm. into the neck. Non-surgical traumatic causes are generally due to stab wounds or explosive fragments. There are also non-penetrating traumatic causes, as for instance, thoracic duct injury during delivery (hyperextension of the spine), injuries with or without fractures and rupture of the thoracic duct secondary to severe cough (sudden change in intrathoracic pressure). With the advent of thoracic surgery in recent years, the number of cases of traumatic chylothorax has increased.

There is another group of cases of non-traumatic etiology. In these cases there is obstruction to the flow of chyle because of intrinsic or extrinsic causes. Intrinsic lymphatic obstruction may be due to neoplasm, thoracic duct thrombosis, filariasis or thrombosis of the jugular or subclavian veins.

Tumors can compress or erode the thoracic duct from the outside. These tumors may take the form of sarcomas, carcinomas, leukemic infiltrates and granulomas such as tuberculosis. The most common variety of carcinoma is metastatic carcinoma from the stomach.

*Anatomy*:

The thoracic duct originates at the cysterna chyli which is on the anterior surface of the second lumbar vertebra. The cysterna chyli receives lymph from the liver, intestine and descending thoracic and lumbar trunks and transports this lymph through the aortic hiatus between the aorta and azygos vein. At the fifth thoracic level, the duct crosses over to the left side and enters the superior mediastinum behind the aortic arch and subclavian artery, between the left side of the esophagus and the left parietal pleura. It is separated from the esophagus by a thick layer of adipose and connective tissue and is bound to the vertebral column by prevertebral fascia. After arching above the clavicle, it joins the internal jugular vein as a single trunk. The only constant valve is at the lymphaticovenous junction. Other valves are variable in number and position.

Embryologically the duct forms as two parallel tubes with numerous cross-anastomoses. The left caudal portion atrophies due to pressure from the aorta and the anastomosis at the level of the fifth thoracic vertebra dilates. Most of the cephalad right duct also atrophies, except for a small segment, approximately one inch in length, which corresponds to the right main lymph trunk. Garamella[11] injected the thoracic duct with 70% iodopyracet in 35 cadavers and followed the course with X-rays. He demonstrated frequent variations in thoracic duct patterns, and suggested that this collateral circulation should allow ligation of the thoracic duct with impunity. This is born out by low incidence of chylous ascites after superior vena cava ligation as reported by Blalock *et al.*[5] and by actual thoracic duct ligation as reported by Klepser.[3]

The diagnosis of chylothorax is based, first upon the demonstration of milky fluid aspirated from the pleural space, having the physical and chemical properties as outlined above. True chyle must be differentiated from other milky appearing fluids might might be termed chyliform or pseudochylous fluid. "Chyliform" refers to a milky fluid due to cellular degeneration such as seen in the break-down of neoplastic tissue. This fluid is low in fat content. "Pseudochylous" refers to fluid which is cloudy because of substances other than fats, such as cellular debris and proteins, seen for instance in empyema.

Chyle has the following characteristics: It is an emulsion of fine fat globules in lymph; it is alkaline; it is sterile on culture; and it resists putrefaction. The specific gravity is greater than that of plasma and the protein content is approximately one-half that of plasma. The total fat varies between 0.5 Gm.% and 3.0 Gm.%, depending upon the dietary fat content. It appears that the greater part of markedly unsaturated fatty acids is absorbed from the digestive tract intact whereas saturated fats and long chain fatty acids are first hydrolyzed and then resynthesized[12]. The total protein may vary between 1.0 and 6.0 Gm.%. Total solids are usually in excess of 4%. The pleural fluid

in our patient conformed to these characteristics.

Clinically, the major symptom of chylothorax is dyspnea. Sometimes the patient may experience a transient episode of shock or collapse which occurs when the fluid ruptures into the pleural space. If the thoracic duct involvement is below the level of the fifth thoracic vertebra, there will be signs of right sided pleural effusion; If above this level, the findings will be those of left sided pleural effusion. Since the thoracic duct courses from right to left at the level of the fifth thoracic vertebra, these clinical variations are understandable.

The most suitable dye for the purpose of demonstrating chylothorax is D & C #6 (Drug and Cosmetic), a green lipophilic coal tar derivative. This is superior to the red dyes since it is not confused with blood. As suggested by Klepser[3], this dye was mixed with butter and fed to the patient. There is no unpleasant taste and therefore it is easily tolerated. Since the color may be offensive to some patients, Klepser[3] has suggested that it be fed in a darkened room. The dye is transported with the fat through the intestinal wall via the lacteals to the thoracic duct. With obstruction to the duct, the labeled chyle penetrates the duct wall and reaches the pleural space. In perforations of the duct, the course is similar. Garamella[11] showed that coal tar dye would color the pleural fluid within forty minutes of administration. Although the dye may also appear in chyliform effusions, in cases of the latter, it is only weakly concentrated as compared to the intense discoloration that appears in true chylous effusions*. The color may be intensified by addition of alkali. Upon addition of ether and subsequent extraction, it will appear in the ether layer.

The immediate treatment of chylothorax is thoracentesis for relief of dyspnea. In addition, the diet should be low in fat and high in protein for two reasons: The low fat decreases the rate of flow of chyle, and the high protein is necessary for nutritional balance. This is especially true if dyspnea continues to be a problem, necessitating frequent thoracenteses. Since fat soluble vitamins are lost in chylothorax, they should be supplied, preferably in the water soluble form. If the fluid continues to reaccumulate in large quantities and the nutritional deficiency becomes pronounced, surgical intervention becomes necessary without delay. The first successful ligation of the thoracic duct was performed by Lampson[7] in 1948 and since that time this procedure has been utilized forty times without a single fatality. In non-traumatic cases, it is equally important to treat the underlying cause.

*In a patient with post-necrotic cirrhosis and chyliform ascites, this was found to be true.[14]

## Summary

A case of reticulum cell sarcoma resulting in true chylothorax was presented. The diagnosis was established by feeding the patient a lipophilic coal tar dye and subsequently this dye was recovered in the thoracic fluid aspirate. The patient responded to treatment with intravenous and intrapleural nitrogen mustard and a course of X-ray therapy. There has been no reaccumulation of fluid for seven months, as of the date of this writing.

* * *

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# IN MEMORIAM

MEYER J. STEINBERG, M.D.
1903 — 1958

It is with great sadness that we note the death of Meyer J. Steinberg, who succumbed to myocardial infarction at the age of 54 on January 6, 1958. He was born in Chicago on August 8, 1903 and lived there except for the last few years of his life, during which he resided on the North Shore. He was educated in Chicago, received a B.S. degree at the University of Chicago in 1923 and an M.D. degree at Rush Medical School in 1927. After interneship at Cook County Hospital he went to Vienna for post-graduate study.

Dr. Steinberg was one of the pioneers in group medical practice in the Middle West, and one of the founders of the Civic Medical Center of Chicago, in which he was active from its inception in 1935 until his death, with the exception of the three years 1942-1945 during which he was in the Armed Forces.

He was Attending Physician at Cook County Hospital, Consultant in Medicine to the Veterans' Administration, and on the medical staffs of Bethany, Edgewater, and Louis A. Weiss Memorial hospitals in Chicago and the Highland Park Community Hospital. He was a valuable member of the faculty of the Chicago Medical School, first as Clinical Assistant Professor of Medicine and then as Clinical Associate Professor of Medicine.

Dr. Steinberg was an extraordinarily fine physician because of the rare combination of a brilliant mind and a sterling character. His loyalty, kindness, warmth, gentleness, modesty, complete integrity, thoroughness, patience and sense of humor endeared him to his host of friends and patients and to those of his colleagues fortunate enough to know him. He was deeply interested in medical education, and was able to inspire his students with some of his own devotion to his profession. His death was a grievous loss to the Chicago Medical School. But even greater than this loss was that sustained by his widow, Bess, his son Martin, and his daughter Judy, with whom he had led an ideal family life, and to whom we extend our profound sympathy. **—Ernest B. Zeisler**

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# MEDICAL EDUCATION*

## The Student, The Teacher, The Patient

MEYER J. STEINBERG, M.D.**

*There is a kind of character in thy life,*
*That to the observer doth thy history*
*Fully unfold*

*—William Shakespeare*

There have been many changes, in this country at least, in medical education since the Flexner report in 1910. The principles underlying newer methods have been repeatedly stated and are still under discussion.

The human elements necessary for a successful, integrated and sound medical education are the patient, the student and the teacher. Philosophical, ethical and sociological precepts and principles motivate the learning and teaching processes.

Medicine is to me more than merely another profession. It is a useful and productive life-work. In this respect similar to religion, it is a way of life which encompasses a reverence for life. Medicine is sacred because its primary objective and principal goal is the preservation and prolongation of life. At present the profession is also working to put life into years. The practice of our profession imposes a responsibility upon each of us to combat disease and suffering, to afford comfort, and to labor for the total improvement of another human being. The good physician, like the religious leader, strives to teach his patient a better way of life, and to better him physically and spiritually.

The study and practice of medicine must be motivated by such human qualities as love of man, respect, compassion, concern, interest, empathy, understanding, patience, loyalty, gentleness, honesty and integrity. In the process of learning and doing, the student and physician will acquire both knowledge and wisdom. To achieve this goal, continuous study, hard work and application to the task at hand are required. A totally disciplined life will result, which should lead to a reward that has no equal in any other profession or art.

The foundation for the development of the good physician or teacher must be laid long before the termination of his college years. A thorough grounding in liberal arts and sciences is vitally essential; this should include the humanities, languages, the arts, literature, history and social science. The study of physical science is important, but does not constitute the whole stock of the "tools of the trade". In a comprehensive survey of medical education, a report of the Subcommittee on Preprofessional Education[1] was made by Severinghaus of Columbia, who said ". . . Preprofessional education

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**Dr. Steinberg died on January 6, 1958. At the time of his death he was Clinical Associate Professor of Medicine, The Chicago Medical School, Chicago, Illinois.

*On the previous page, there appears the obituary of Dr. Meyer J. Steinberg, written by Dr. Ernest Zeisler, a close friend and life-long associate of Doctor Steinberg. An even more fitting tribute to this fine physician, dedicated teacher and outstanding human, ironically, was penned by his own hand. A few days before his final illness, Doctor Steinberg asked me to read a manuscript which he was preparing for publication in this journal. I read and enjoyed the paper, but before I could offer a few minor suggestions, he was fatally stricken. The manuscript appears, therefore, in what Doctor Steinberg had considered an early draft. Nevertheless, it is clearly much more than a detached essay on medical education. It is a credo containing distilled wisdom, glowing conviction and a profound sense of responsibility — an innocently written obituary, poignant in its timeliness.*

—HYMAN J. ZIMMERMAN, M.D.

should also include 1) an accurate and felicitous use of the language, 2) constant interest in knowledge about man, his society, and the world, 3) training in mature and responsible evaluation and decision in the controversial areas of social policy, morality, religion, and art, 4) training in synoptic comprehension—the escape from the multiple provincialisms which bedevil mankind, and 5) the attainment of larger and more inclusive perspectives." In another interim report he wrote under the caption of "Responsibilities of Education"[2]: "We do, however, state with firm conviction that . . . it is as much the responsibility of education to assist students to develop proper attitudes as to develop competence. To what ends competent men and women will direct their efforts depends upon their sense of values, and education must deal with value judgments. . . . The academic disciplines must join in offering to every liberal arts student the opportunity to know himself better to appreciate his own place in society and the relation of his society to the total world order . . . and finally, to acquire a comprehensive view of life and perspectives through which he becomes emotionally stable and soundly motivated, a happy and effective citizen . . . to focus attention on what we have found to be the more important areas of interest and concern in liberal arts education."

Upon entering the clinical phase of his medical education, the student must have thorough grounding in the biological basic sciences: anatomy, embryology, physiology, pharmacology, biochemistry, bacteriology, and psychology. He should be particularly aware of man's relationship to other people, his family, his work, his community and the emotional stresses, strains, anxieties, and fears to which man is daily subjected. Emphasis should constantly be placed on the scientific attitude which encourages honesty and integrity in the search for truth. In the case of the medical student it is the inquiring mind, the alert eye, the sensitive ear and the careful recording of data—the "pen, pencil and notebook," habits which, constantly nurtured, produce an adequate and finished product. The student must be constantly reminded and corrected to train himself to make logical and unprejudiced deductions by knowing what elements go into the making of a satisfactory clinical report or experiment, the necessity for proper sampling, adequate controls and the care necessary in drawing conclusions. He must be critical of everything he hears or reads, and he must constantly sort out and select the good from the bad, the valid from the questionable. In these days with such a voluminous medical literature, requiring constant and daily perusal, he must be discriminating. He must develop good study habits. He should guard against being swallowed by the mass of writing which is "ground out" every day.

### The Student and the Patient

It is in relation to the patient that the student gets his first opportunity to develop the clinical skills that are so important in his medical education. The understanding of disease begins with the approach of the student to the patient, development of a good technique in obtaining a history of the illness and the performance of a careful and thorough physical examination. In taking the history two important factors are frequently neglected; first, a realization that the patient who is being questioned is a human being who has a story to tell and a diagnosis to offer if he is given the opportunity to talk and is not bombarded with direction questions; secondly, that much information of importance in the diagnosis and subsequent treatment of the patient can be obtained by indirect questioning. The patient's reaction to past events in his life are often a clue as to what ails him at the present time.

The physical examination of a patient begins the moment the student approaches the patient. As the history is being taken, an alert eye, a sensitive ear, a gentle touch and an understanding heart may give all the information necessary, whereas hundreds of dollars worth of laboratory tests will only confuse the clinical picture. The art of medicine is not merely a good bedside manner, but thorough clinical study. Basic knowledge



PHILOMATH MEDICINE AS A LIBERAL ART

combined with proper evaluation of the information collected will lend to correct diagnosis and successful treatment. A kind and friendly greeting will repay a student and a physician in many ways. The proper approach to a suffering, miserable human being is most essential. A patient's faith, respect and warm regard for the physician will develop when the patient feels that his doctor has sincere interest and concern for him, and to this end a confident and gentle approach will be found to be of great help.

Once a close relationship has been established between the patient and the student, the latter must be on guard that the patient does not substitute him for the physician who is responsible for the patient's care. It frequently happens that the patient begins asking the student many questions relating to his illness. The student must cautiously sidestep answering them because he is not as yet prepared to assume this responsibility. He must defer the answers to his superior, who may be the interne, resident, or the attending physician. The student should not discuss the patient's illness with the patient's relatives. Conferences or discussions about the diagnosis, prognosis, and treatment in general should be held out of earshot and out of sight of the patient. Unless something favorable or optimistic in a general sense can be said in front of the patient, it is better that nothing at all be said. A disease with a bad prognosis or one requiring radical treatment should never be mentioned in front of the patient. Patients misinterpret what we say, and understand much more than we realize. They often look up terms they do not understand and are mostly unprepared for the shock of learning about a particular illness.

The hospital room, ward or corridor is a place for quiet, serious, and sober behavior. The student must be clean, neat, restrained, orderly, and must radiate a feeling of cheerfulness. The bedside or ward is not a place for noisy discussion or practical jokes.

**The Student and the Teacher**

The student should accord his teacher respect and courtesy. Questioning an opinion or a statement for the purpose of learning or clarification is the student's privilege, but there is never an excuse for doing this in other than a courteous and gentlemanly manner. The question should be carefully thought out so that the answer can be properly given. Any answer that is received should be carefully evaluated as to source, adequacy, and reliability. In medicine, as in many other spheres, there is room for honest differences of opinion.

In the "old days" instances of overt disrespect or discourtesy rarely occurred in the teacher-student relationship. (And I hasten to add that the teachers in those days were no better than today.) When such an instructor walked up to a group at the bedside or into a conference room, silence would fall and the group or class would "come to attention". Students in small groups at the bedside would stand while waiting for the instructor to speak and would not sit down unless he invited them to do so. Strict attention was paid to what was being said or done, and separate discussions among the students did not take place while a student or instructor was speaking or demonstrating a clinical feature. Punctuality and regularity of attendance was mandatory. These requirements were in no way intended to interfere with freedom of expression or action, but only to show that anarchy of any type, even intellectual, was unhealthy and had no place in the learning process. Much more could be said about the behavior of the student, but I leave the rest to the student.

The good teacher knows that the quality of his teaching must steadily improve. The fact that a man or woman has achieved professional eminence in research, practice or administration does not necessarily assure his adequacy for the responsibility of teaching. In an investigative analysis of educational principles, twelve members of the faculty of the University of Buffalo School of Medicine spent twenty hours with another member of the faculty trained in sociology and anthropology who had a special interest in the dynamics of learning. In a report of their experience, Dr. George E. Miller[3] gave the following

summary: "1) People learn what they want to learn. 2) Knowledge and learning are different. The things that we retain are those which arouse our emotions such as curiosity, anger, disagreement, laughter, etc. Facts or knowledge are not to be possessed—they should possess us." Knowledge when properly utilized is the core of education and the flame of wisdom. It is never too early to begin to impress upon the student, the techniques which aid him in the utilization of his knowledge.

The teacher is often not conscious enough of the fact that he resists change, and uses various techniques to support himself in defending his opinion. The student must be given full freedom to question and challenge. It is not by conformity but by dissent that learning proceeds and grows. Teachers, in general, have accumulated considerable information, and have supposedly learned the most effective ways of imparting that information to the student. Every teacher unconsciously projects an image of himself in the teaching process, and expects the good student to give the answer he wants, which is assumed to be the right answer. Learning, however, begins not with complete unanimity and agreement, but when the answer is unknown, and when there is difference of opinion, dissent and question. Why these differences exist seems to me to be the core of the process of education. As stated by Dr. Miller[3], "How can they believe we encourage independence, when in biochemistry they are taught to reply that diabetes is the result of an overproduction of glucose while in physiology it is due to underutilization, and when in pediatrics only Digitoxin can be used to treat congestive heart failure and in medicine only whole leaf of digitalis? If they ask why these things are so, they are told in essence, 'Because I say so.' Not this crudely I grant. But if one listens to tones, to shadings, to the meanings that words conceal rather than the words themselves, it becomes evident how rarely a teacher allows the image of himself to be threatened. Instead we use students to support this image. We expect them to defer to us, to respect and admire us, to mimic us, and to do well when examined by others on the material we are presumed to have taught them. . . . The professional responsibility of the teacher should be obvious. It is based upon a fundamental respect for the individual student, an awareness of the dynamics of learning that must allow each student to be different and that encourages challenge. It is concerned with helping the student to want to learn rather than to know. It involves an honest effort to understand the student rather than to judge him. This should be easier for the physician-teacher to understand than almost any other. The physician's occupation is to provide a professional service to patients. He attempts to understand their problems and to be of use in their solution. He makes no moral judgment of the illness and suffers no offense or loss of prestige if the patient ignores his advice or fails to respond to his best therapeutic efforts. He is secure in his role. It is this kind of professional service that the teacher owes the student, . . .

"While this indictment is broad, it does not include all medical teachers. And, of those it does embrace, a significant number might say that they would like to teach in this understanding, challenging encouraging way but are forced by departmental policy, curriculum arrangement, state and national board examinations, or some other restriction to conduct themselves in an orthodox, authoritarian fashion that they recognize as second rate. This brings me to the final point, the nature of the compromise. There are realities that we all must face. There are limits beyond which we cannot go, limits of time and space, external and internal forces that must be respected. To recognize such limitations, however, is quite different from using them as an excuse for not doing something you really do not want to do anyway. As Cantor puts it, 'Even in a straightjacket there is room for some movement.' We do what we can when we can do it. But first we must understand ourselves."

The teaching of clinical clerks, or clinical clerkship, has become popular in medical teaching. By this method the



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student comes into actual contact with the patient, assumes a limited responsibility under guidance, and learns through his individual effort and discussion. Unless education is considered as learning to put knowledge to use,[4] the teacher will fail to go beyond what can be gained by ward rounds and lectures. In a paper on "A Philisophy for Clinical Clerks," Cotsonas[4] writes, "The culmination of this case study is the presentation of the case to and its review with an instructor. This instructor has a great responsibility to the student; he must sustain the student's motivation within the case study method. If he contents himself with criticizing the write-up and discussing diseases and articles with the student, the case study method is defeated and student motivation suffers. If this is truly an exercise in principles, he will show interest in the student's thinking as reflected in his work-up and explanation of the problem as the student has attempted to visualize it for himself. He will require the student to justify his determination or circumscribing of the problem—what was he after, why was he after it, and what did he do with what he discovered. The reason why he read about these particular diseases and articles rather than merely an investigation of the articles and diseases themselves should be discussed. This attention to 'why' not only sustains student motivation within this philosophy, it becomes an evaluation of the student's reasoning as well as his knowledge of facts. The evaluation is an important teaching technique as a prelude to teaching and learning. For, in the discussion which results from the student's defense of 'why,' the student has the opportunity to understand the reasons for the differences between his own thinking and that of the instructor, as well as to incorporate any facts the instructor utilized or introduced. This true participating relationship compels the student to give up his usual self-protective preclinical desire for anonymity. It ceases to be so important not to be wrong as it is important to have the opportunity to learn from one's mistakes. A student need never fear being wrong in this situation as long as it is obvious he tried very hard, for this then becomes a learning session. And a teaching session would be incomplete until the teacher had made an additional contribution by taking the student beyond his knowledge."

The patient, the student, the physician-teacher can all take part in a wonderful intellectual and emotional experience. From this mankind as a whole should benefit.

Learning begets knowledge, knowledge should lead to wisdom. And wisdom is what the whole world needs right now.

# ABSTRACTS SECTION

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Recent Progress in Hormone Research, Vol. XIII, 1957, Academic Press, Inc., New York, N. Y.

GLUCAGON, A SECOND PANCREATIC HORMONE. P. P. Foa, Giorgio Galansino, and Guido Pozza. The evidence summarized in this paper suggests that Glucagon is a potent, quick-acting hormone capable of stimulating liver glycogenolysis and, hence, of raising the blood sugar concentration and depleting liver glycogen. Glucagon appears to be secreted by the alpha cells of the islets of Langerhans in response to hypoglycemia and, possibly, to stimulation by anterior pituitary growth hormone. Glucagon is secreted into the portal system and reaches the liver directly. This is in contrast with epinephrine, which also causes hyperglcemia by promoting liver glycogenolysis but reaches the liver only after having been diluted in the general circulation and, in great part, oxidized. Thus glucagon, because of its potency, its site of production, and the lack of side effects, is ideally suited suited for the correction of the daily physiologic fluctuation in blood sugar level. Marked hypoglycema, on the other hand, would result not only in the secretion of glucagon, but also of pituitary and adrenal cortical anti-insulin hormones and of sufficient epinephrine to reach the liver in significant amounts. In considering how glucagon protects the organism against the dangers of hypoglycemia by getting glucose out of its readily available store in the liver, one is reminded of the similar role of parathyroid hormone in protecting the organism against the danger of hypocalcemia by getting calcium out of its readily available stores in the bone. The possibility that glucagon, acting on liver glycogen, may help regulate the concentration of plasma potassium should be investigated. Other actions of glucagon, in particular its effect on glucose utilization and its role in diabetes, are too uncertain to allow definite conclusions and should also be investigated further. For these reasons it is better to avoid semantic difficulties and postpone the classification of glucagon as an antagonist, a synergist, or a regulator of insulin action.

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PULMONARY REFLEXES IN PULMONARY EDEMA: Oravanes, C. A., Librette, E.; Jona, J. F.; Polly, C. K. Lui, and Luisada, A. A., The Chicago Medical School. Am. J. Physiol. 189 (1): 132-136, 1957.

The mechanism of pulmonary edema caused by stimulation of the central nervous system was studied in 33 dogs. Stimulation was obtained by the intrasisternal injection of veratrine, or of air or saline under high pressure, or by electric stimulation of the hypothalamus. Pressure changes in the pulmonary artery, left atrium and left ventricle were recorded by means of three catheters introduced through the right external jugular vein and the left femoral artery

Experiments were performed with closed or open chest, and following ligation of the thorasic aorta and inferior cava. Lung capacity was studied as a means to estimate the blood content of this organ. Data obtained in closed chest experiments suggest that a blood shift from the systemic to the pulmonary circulation may be a factor in veratrine induced pulmonary edema. This was confirmed by the observation that following mechanical exclusion of the systemic circulation, no pulmonary edema occurred while the changes of left ventricular pressure were minimal and inconstant.

In these animals, pulmonary artery pressure still rose indicating vasoconstriction while an increase of lung capacity suggested that the vasoconstriction was greater in the pulmonary veins than in the arteries. Injection of air or saline under high pressure into the cisterna magna and faradic stimuation of the hypothalamus caused pulmonary hypertension, even after exclusion of the systemic circulation. In these experiments, a decreased lung capacity suggested that the pulmonary constriction was greater on the arterial side than on the venous side.

These findings are offered as evidence that the caliber of the pulmonary vessels may be influenced by central nervous system stimulation, an additional element to be considered in the mechanism of pulmonary edema.

M.J.B.

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MUTE, MITRAL STENOSIS, MYCARDIAL INFARCTIONS, AND ISCHEMIC GANGRENE IN OLD AGE—CASE REPORT, by C. Arovanis, M.D., Div. of Cardiology of The Chicago Medical School, and Mount Sinai Hospital. Angiology, vol. 8, n. 2, April, 1957. pp. 188-195.

An unusual case of associated cardiovascular disease is presented. A 64 year old diabetic arteriosclerotic and hypertensive patient had an episode of pulmonary edema and vascular collapse followed by bilateral gangrene of the lower limbs. A second episode caused death.

Autopsy revealed: (1) rheumatic heart disease and tight mitral stenosis; (2) coronary heart disease and an old and recent infarct; (3) left atrial thrombosis resulting in multiple embolisms (one old cerebral; one recent—of the iliac arteries); and (4) arteriosclerosis obliterans.

Mitral stenosis was silent, as proved by auscultation and phonocardiography. Electrocardiography failed to undisputedly reveal the infarcts (one was old; the other, terminal). Surgery showed that the gangrene was not due to embolism ( a saddle or double embolus took place only in the terminal stage).

L.K.

PHYSIOLOGIC MEDIATION OF PSYCHIC STIMULI IN DIABETES MELLITUS, by P. P. Foa, Intl. Res. Med. 170, n. 10, October, 1957. pp. 576-581.

The hypothalamus oppears to mediate the somatic manifestations of emotions, not only by regulating autonomic reactions such as pallor, blushing, tachycardia, rise in blood pressure, sweating, tremors, and increased smooth muscle activity, but also by activating the endocrine system. In this manner, anxiety and other psychodynamic forces may cause somatic changes, and precipitate or aggravate acute or chronic illness, the awareness of which may, in turn, become a source of anxiety..

The participation of the hypothalamo-hypophysical system, capable of regulating a multitude of functions, may explain the great variety of organic and functional changes that can be precipitated by psychogenic stimuli and offers hope for a better understanding not only of the relationships between psychoendocrine and other psychosomatic phenomenon but of psychologic processes in general.

L.K.

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THE L.E. PHENOMENON IN RHEUMATOID ARTHRITIS by Irving A. Friedman, M.D.; Jerome F. Sickley, M;..D Robert M. Poske, M.D.; Arnold Black, M.D.; David Bronsky, M.D.; Wilson H. Hurtz, Jr., M.D.; Charlotte Feldhake, B.S.; Paul S. Reeder, M.D., and EliM. Katz, M.D.

This article presents a study of the largest series of patients with positive L.E. preparation and the relation of the L.E. prepration to rheumatoid arthritis. The L.E. phenomenon was found in 25 of 91 patients presenting the classic clinical picture of rheumatoid arthritis. Therapy did not influence the incidence of positive preparations in the study. Rheumatoid nodules, Felty's syndrome and an elevated electrophoretic gamma globulin occurred more frequently in the group with the positive L.E. preparations. None of the patients presented pure rheumatoid spondylitis. The patients with the positive preparations were otherwise similar to the patients with negative preparations. Pathognomonic features of systemic lupus erythematosus were not observed in any patient. It is concluded that the L.E. phenomenon may occur in patients with rheumatoidal arthritis as a nonspecific reaction. The diagnosis of systemic lupus erythematosus in such patients, therefore, should be based upon the criteria.

G.B.M.

LACTIC DEHYDROGENASE AND GLUTAMIC OXALOACETIC TRANSAMINASE IN NORMAL PREGNANT WOMEN AND NEWBORN CHILREN, by Michael West, M.D., and Hyman J. Zimmerman, M.D. Am. J. Med. Sc., Vol. 235, No. 4, April, 1958.

The lactic dehydrogenase and glutamic oxaloacetic transaminase levels were studied in 70 women representing the 3 stages of pregnancy. Two slightly elevated lactic dehydrogenase levels were noted. No glutamic oxaloacetic transaminase elevations were found. In fact, the glutamic oxaloacetic transaminase levels of this enzyme were generally lower than the average adult level.

Twenty-seven women were studied during labor. Eleven of these patients had elevated L.D. levels, only 2 of which were marked. Only one borderline transaminase elevation was noted in this group.

Cord blood from 19 infants was studied. The lactic dehydrogenase levels were elevated (above 270) in the cord blood in 18 of 19 newborns studied. The transaminase levels ranged from 9 to 52 in 17 of these. In the remaining 2, the levels were 113 and 114 units respectively.

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STIMULATION OF INSULIN OUTPUT BY MONOSACCHARIDES AND MONOSACCHARIDE DERIVATIVES. Guido Pozza, Giorgio Galansino, Harvey Hoffeld and Piero P. Foa. From The Department of Physiology and Pharmacology, The Chicago Medical School, Chicago 12, Illinois. Amer. J. Physiol. 192; pg. 497:1958.

The ability of various sugars and closely related substances to stimulate insulin secretion was studied by means of pancreatic-femoral cross-circulation experiments between hepatectomized donor dogs and normal recipients. In other experiments, the test substance was injected directly into the pancreatic artery of normal dogs. The administration of d-glucose, d-galactose or d-ribose was followed by a prompt hypoglycemia, suggesting insulin secretion; d-arabinose caused an unexplained delayed hypoglycemia, while d-fructose, d-mannose, d-xylose, l-arabinose, 3-methylglucose, d-glucosamine, galacturonic acid and saline had no effect. The tentative hypothesis that insulin secretion is stimulated by sugars which are both utilizable and insulin-sensitive is offered. No relationship between chemical structure and ability to cause insulin release was found.

CONDITIONAL FEATURES OF SOUND-EVOKED EEG RESPONSES DURING SLEEP. J. E. P. Toman, I. M. Bush and J. T. Chachkes. *Federation Proceedings*, Vol. 17, No. 1, Part 1; 1958

The following experiments in human subjects suggest that sleep is characterized by a more profound depression of conditioning mechanisms than of discriminations based on previous conditioning, and further suggest that alleged conditioning during sleep can occur only insofar as the reverberating stimulus trace persists through a minimum period of making. Brief verbal stimuli were delivered at intervals of 20 seconds to subjects during daytime sleep at a level below dreaming where the EEG K-complexes could be elicited. Trace recall tests after awakening showed no significant retention even after considerable repetition unless there was an appreciable period of wakeful EEG, 5 seconds or more, following one such stimulus. Nevertheless "loaded" words such as the subject's nickname were consistently more effective than "unloaded" physically equivalent words in causing spread and prolongation of EEG change, even though such words were not subsequently remembered. The relative prominence of the K-complex in man compared to laboratory animals, its absence in man in the dreaming stage, its tendency toward attenuation on repetition in normal and psychotic subjects are suggestive of a condition discriminative inhibitory mechanism intervening between primary stimuli and primitive alerting mechanisms.

SEXUAL DEVELOPMENT OF MALE RATS TREATED WITH CORTISONE, by Russel O. Hanson, Ben B. Blivaiss, and Robert E. Rosenzweig, The Chicago Medical School. An. J. Physiol. 188 (2): 281-286, 1957.

Immature male rats were treated with 1.0 mg. cortisone acetate daily for 2-4 weeks, starting at 23 days of age, and were maintained on *paired* or *ad libitum* feeding regimes. Body, adrenal and thymus weight were reduced as compared to control animals. Actual test weights were usually reduced less than body, liver or kidney weights. The ratios of testicular to body weight were significantly increased in the animals autopsied at the end of treatment. Histological examination of the testes revealed no significant alterations from normal. The ratios of seminal vessicle and ventral prostate weight to body weight were significantly decreased in all groups of ad libtum-fed animals, and the pair-fed group autopsied at the end of 2 weeks of treatment. There were no significant changes in the other pair-fed groups. No modifications were observed in the histology of these organs.

Pituitary glands removed from pair-fed animals at end of treatment with cortisone for 2 weeks, appeared to have a higher GTH content than in controls as indicated by the growth of the ovaries of immature rats injected with suspension of these glands. Pituitary glands taken from other pair-fed groups and from all ad libitum-fed groups usually showed a lesser GTH content than for controls. H.T.B.

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